

AMERICAN JOURNAL OF DISEASES OF CHILDREN CUK-HO1332-12-P024253

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AMERICAN JOURNAL OF DISEASES OF CHILDREN

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- Geller RJ, Fisher JG: The role of symptomatic therapy for the common cold. J Respir Dis 1987;8(1):20-34.
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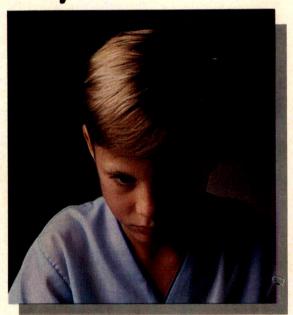
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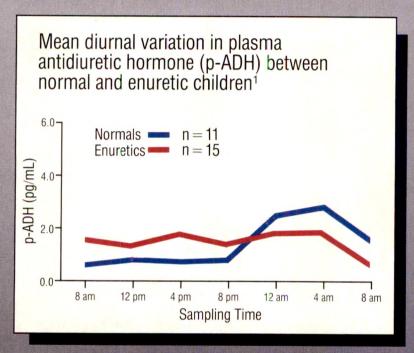
Landmark study now explains why Jimmy can't spend the night away from home



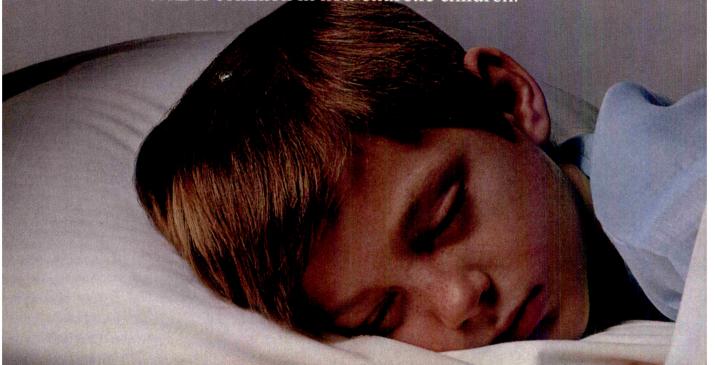
Jimmy is a bed wetter.

New study results indicate that he may have a physiologic problem.

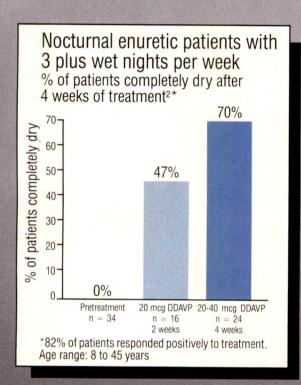
The ADH Deficit



Landmark study concludes: Enuretic children may lack diurnal rhythm of ADH common in non-enuretic children.¹



Announcing the first physiologic treatment for nocturnal enuresis



- DDAVP Nasal Spray, a synthetic analog of naturally occurring ADH, provides physiologic control of nighttime urine production in children 6 years of age or older¹⁻⁴
- Clinically proven in all degrees of nocturnal enuresis, even in many patients resistant to imipramine and alarms³
- Easy for children to use metereddose nasal spray administered at bedtime
- Outstanding safety record in patients of all ages⁵

DAMP Nasal Spray (desmopressin acetate)

Safely Corrects the ADH Deficit

Please see next page for full prescribing information.



Safely Corrects the ADH Deficit

DDAVP Masal Spray Sig. 20-40 mcg intranasally at bedtime for nocturnal enuresis Disp. * 1 5.0 ml Pottle.

DESCRIPTION: DDAVP (desmopressin acetate) is an antidiuretic hormone affecting renal water conservation and a synthetic analogue of 8-arginine vasopressin. It is chemically defined as follows:

Mol. wt. 1183.2

Mol. wt. 1183.2 Empirical formula: C.,H.,IN,,O.,S., SCH,CH,CO-Tyr-Pne-Gin-Asn-Cys-Pro-D-Arg-Gly-NH, • C.,H.O., • 3H,O 1/3-mercaptopropionic acid)-8-D-arginine vasopressin monoacetate (salt) trihydrate.
DDAVP is provided as a sterile, aqueous solution for intranasal use. Each mL contains:
Desmopressin acetate

Sodium Chloride . 5.0 mi
Hydrochloric acid to adjust pH to approximately 4 9.0 m;
The DDAVP compression pump delivers 0.1 mL (10 mcg) of DDAVP per spray.

CLINICAL PHARMACOLOGY: DDAVP contains as active substance 1-(3-mercaptopropionic acid) -8-Darginine vasopressin, which is a synthetic analogue of the natural hormone arginine vasopressin. One mL
(0.1 mg) of DDAVP has an antidiuretic activity of about 400 IU; 10 mcg of desmopressin acetate is equivalent
to 40 IU.

to 40 U.

1. The biphasic half-lives for DDAVP were 7.8 and 75.5 minutes for the fast and slow phases, compared with 2.5 and 14.5 minutes for lysine vasopressin, another form of the hormone used in this condition. As a result, DDAVP provides a prompt onset of antidiuretic action with a long duration after each administration. 2. The change in structure of arginine vasopressin to DDAVP has resulted in a decreased vasopressor action and decreased actions on visceral smooth muscle relative to the enhanced antidiuretic activity, so that clinically effective antidiuretic obess are usually below threshold levels for effects on vascular or visceral smooth muscle. 3. DDAVP administered intranasally has an antidiuretic effect about one-tenth that of an equivalent dose administered by vinection.

muscle 3. DDAVP administered intranasally has an antidiuretic effect about one-tenth that of an equivalent dose administered by injection.

INDICATIONS AND USAGE:

Primary Nocturnal Funresis: DIAVP is indicated for the management of primary nocturnal enuresis. It may be used alone or adjunctive to behavioral conditioning or other non-pharmacological intervention. It has been shown to be effective in some cases that are refractory to conventional therapies.

Central Cranial Diabetes insipidus and for management of the temporary polyuria and polydipsia following head trauma or surgery in the pituitary region. It is ineffective for the temporary polyuria and polydipsia following head trauma or surgery in the pituitary region. It is ineffective for the treatment of nephrogenic diabetes insipidus. The use of DDAVP in patients with an established diagnosis will result in a reduction in urinary output with increase in urine osmolality and a decrease in plasma osmolality. This will allow the resumption of a more normal lifestyle with a decrease in urinary frequency and nocturia.

There are reports of an occasional change in response with time, usually greater than 6 months. Some patients may show a decreased responsiveness, others a shortened duration of effect. There is no evidence this effect is due to the development of binding antibodies but may be due to a local inactivation of the peptide Patients are selected for therapy by establishing the diagnosis by means of the water deprivation test, the hypertonic saline infusion test, and/or the response to antidiuretic hormone. Continued response to DDAVP can be monitored by urine volume and osmolality.

DDAVP is also available as a solution for injection when the intranasal route may be compromised. These situations include nasal congestion and blockage, nasal discharge, atrophy of nasal mucosa, and severe atrophic rhinitis. Intranasal delivery may also be inappropriate where there is an impaired level of consciousness. In addition, cranial surgical procedures, such as

trom surgery.

CONTRAINDICATION: Known hypersensitivity to DDAVP

WARNINGS: 1. For intranasal use only.

2. In very young and elderly patients in particular, fluid intake should be adjusted in order to decrease the potential occurrence of water intoxication and hyponatremia.

2. In very young and elderly patients in particular, fluid intake should be adjusted in order to decrease the potential occurrence of water intoxication and hyponatremia.

PRECAUTIONS:

General DOAPV at high dosage has infrequently produced a slight elevation of blood pressure, which disappeared with a reduction in dosage. The drug should be used with caution in patients with coronary artery insufficiency and/or hypertensive cardiovascular disease because of possible rise in blood pressure.

Central Cranial Diabetes Insipidus: Since DDAVP is used intranasally, changes in the nasal mucosa such as scarring, edema, or other disease may cause erratic, unreliable absorption in which case intranasal DDAVP instruction should be considered.

Primary Noctumal Enuresis: If changes in the nasal mucosa have occurred, unreliable absorption may result. DDAVP intranasal solution should be discontinued until the nasal problems resolve.

Information for Patients: Patients should be informed that the bottle accurately delivers 50 doses of 10 mcg each. Any solution remaining after 50 doses should be discarded since the amount delivered thereafter may be substantially less than 10 mcg of drug. No attempt should be made to transfer remaining solution to another bottle. Patients should be instructed to read accompanying directions on use of the spray pump carefully before use.

Laboratory Tests: Laboratory tests for following the patient with central cranial diabetes insipidus or post-surgical or head trauma-related polyuria and polydipsia include urine volume and osmolality, in some cases plasma osmolality may be required. For the healthy patient with primary nocturnal enuresis, serum electrolytes should be checked at least once if therapy is continued beyond 7 (ays.

DRUG INTERACTIONS: Although the pressor agents should only be done with careful patient monitoring.

CABCINGENESUS MITAGENESUS MITAGENESUS MPAIRMENT OF FERBILITY: Teratology studies in rats have shown no

monitoring. CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Teratology studies in rats have shown no

MONITORING.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Teratology studies in rats have shown no abnormalities. No further information is available.

PREGNANCY—CATEGORY B: Reproduction studies performed in rats and rabbits with doses up to 12.5 times the human intranasal dose (i.e. about 125 times the total adult human dose given systemically) have revealed no evidence of harm to the fetus due to desmogressin acetate. There are several publications of management of diabetes insipidus in pregnant women with no harm to the fetus reported; however, no controlled studies in pregnant women have been carried out. Published reports stress that, as opposed to preparations containing the natural hormones, DDAVP (desmogressin acetate) in antidiuretic doses has no uterotonic action, but the physician will have to weigh possible therapeutic advantages against possible dangers in each individual case.

NURSING MOTHERS: There have been no controlled studies in nursing mothers. A single study in a post-partum woman demonstrated a marked change in plasma, but little if any change in assayable DDAVP in breast milk following an intranasal dose of 10 mcg.

PEDIATRIC USE: Primary Nocturnal Furnesis: DDAVP has been used in childhood nocturnal enuresis. Short-term (4-8 weeks) DDAVP administration has been shown to be safe and modestly effective in children aged 6 years or older with severe childhood nocturnal enuresis. Adequately controlled studies with intranasal DDAVP in primary nocturnal enuresis have not been conducted beyond 4-8 weeks. The dose should be individually adjusted to achieve the best results.

Central Cranial Diabetes Insipidus: DDAVP has been used in children with diabetes insipidus. Use in infants and children will require careful fluid intake restriction to prevent possible hyponatremia and water intoxication. The dose must be individually adjusted to the patient with attention in the very young to the danger of an

extreme decrease in plasma osmolality with resulting convulsions. Dose should start at 0.05 mL or less. Since the spray cannot deliver less than 0.1 mL (10 mcg), smaller doses should be administered using the nasal tube delivery system. Do not use the nasal spray in pediatric patients requiring less than 0.1 mL (10

mcg) per dose.

There are reports of an occasional change in response with time, usually greater than 6 months. Some patients may show a decreased responsiveness, others a shortened duration of effect. There is no evidence this effect is due to the development of binding antibodies but may be due to a local inactivation of the peptide.

ADVERSE REACTIONS: Infrequently, high dosages have produced transient headache and nausea. Nasal congestion, thinitis and flushing have also been reported occasionally along with mild abdominal cramps. These symptoms disappeared with reduction in dosage. Nosebleed, sore throat, cough and upper respiratory infections have also been reported.

The following table lists the percent of patients having adverse experiences without regard to relationship to study drug from the pooled pivotal study data for nocturnal enuresis.

	PLACEBO (N=59)	DDAVP 20 mcg (N=60)	DDAVP 40 mcg (N=61)
ADVERSE REACTION	<u>%</u>	%	%
BODY AS A WHOLE Abdominal Pain	0		
Asthenia	Ö	2	2 2 2 5
Chills	Ŏ	Õ	2
Headache	0 0 2	0 2	5
Throat Pain	2	ō	Ö
NERVOUS SYSTEM			
Depression	2	0	0
Dizziness	Ō	Ō	0 3
RESPIRATORY SYSTEM			
Epistaxis	2	3 2 0 8	0
Nostril Pain	0	2	0
Respiratory Infection	2 2	0	0
Rhinitis	2	8	3
CARDIOVASCULAR SYSTEM			
Vasodilation	2	0	0
DIGESTIVE SYSTEM			
Gastrointestinal Disorder	0	2	0
Nausea	0	0	2
SKIN & APPENDAGES			
Leg Rash	2 2	0	0
Rash	2	0	0
SPECIAL SENSES	0	0	0
Conjunctivitis	0	2 2 0	0
Edema Eyes	Ů,	2	0 2
Lachrymation Disorder	U	U	2

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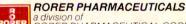
DVERDOSAGE: See adverse reactions above. In case of overdosage, the dose should be reduced, frequency of administration decreased, or the drug withdrawn according to the severity of the condition. There is no known specific antidote for DDAVP. An oral LD_{so} has not been established. An intravenous dose of 2 mg/kg in mice demonstrated no effect.

DOSAGE AND ADMINISTRATION: Primary Nocturnal Enuresis: Dosage should be adjusted according to the individual. The recommended initial dose for those 6 years of age and older is 20 mcg or 0.2 mL solution intransally at bedtime. Adjustment up to 40 mcg is suggested if the patient dose not respond. Some patients may respond to 10 mcg and adjustment to that lower dose may be done if the patient has shown a response to 20 mcg. It is recommended that one-half of the dose be administered per nostril. Adequately controlled studies with intransal DDAVP in primary nocturnal enuresis have not been conducted beyond 4-8 weeks. Central Cranial Diabetes Insigidus: DDAVP dosage must be determined for each individual patient and adjusted according to the diurnal patient or response. Response should be estimated by two parameters: adequate duration of sleep and adequate, not excessive, water turnover. Patients with nasal congestion and blockage have often responded well to DDAVP. The usual dosage range in adults is 0.1 to 0.4 mL daily, either as a single dose or divided into two or three doses. Most adults require 0.2 mL daily in two divided doses. The morning and evening doses should be separately adjusted for an adequate durnal rhythm of water turnover. For children aged 3 months to 12 years, the usual dosage range is 0.05 to 0.3 mL daily, either as a single dose or divided into two otses. About 1/4 to 1/3 of patients can be controlled by a single daily dose. The masal dosped and only deliver doses of 0.1 mL 10 mcg or multiples of 0.3 mL L11, with the oral patient than these are required, the nasal tube delivery system may be used.

HOW SUPPLIED: A 5 mL bottle

Rev. 6/89

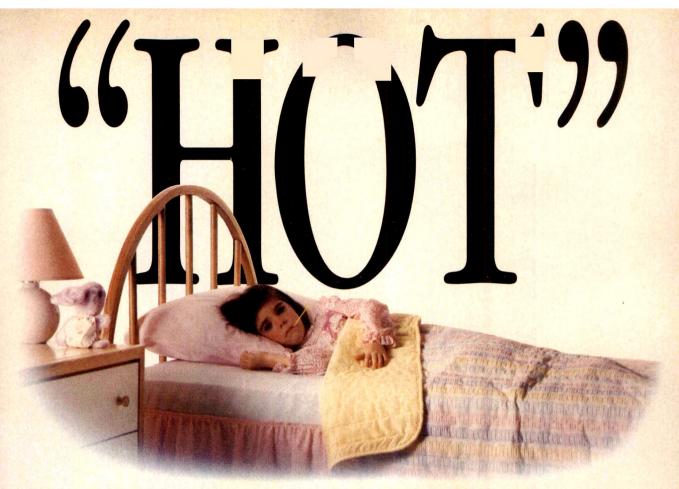
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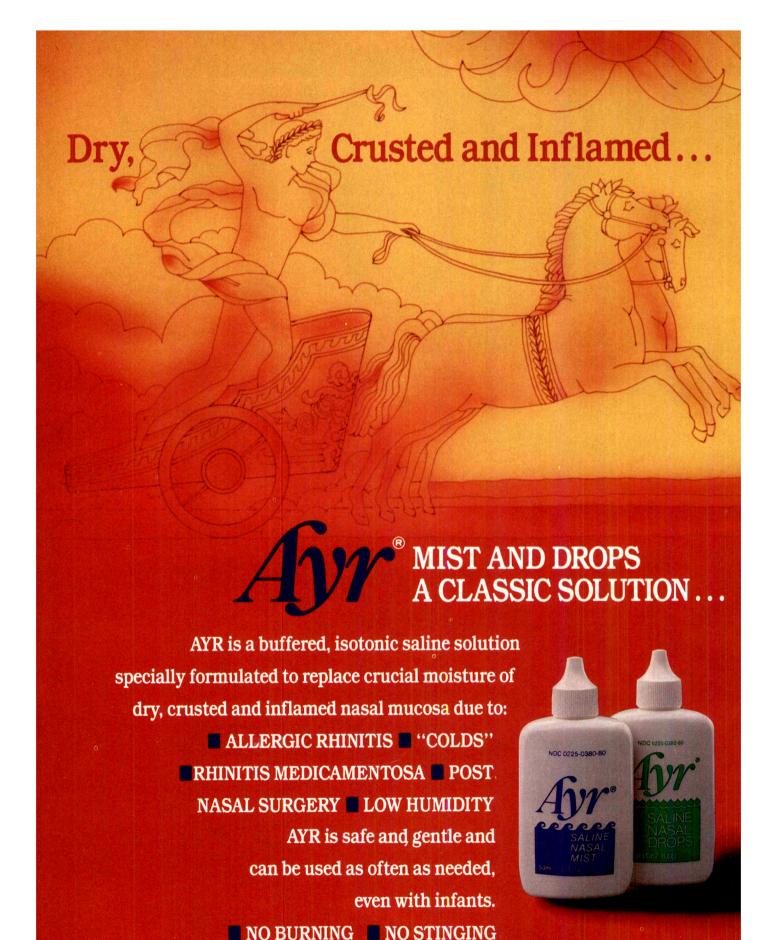
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Is Standard Practice 'Standard' In **Community Pediatrics?**

Sir.-Dr Fulginiti¹ made some good points in his editorial in the May issue of AJDC on standards. Having sat on several committees that grappled with establishing standards, I feel that it also is important to recognize some of the inherent biases of such committees. First, they tend to agree there is a problem requiring the establishment of a standard. Second, they are biased toward a "safe rather than sorry" viewpoint. Third, they do not reflect the universe of those who deal with the problem. Rather, they tend to reflect those who see the worst aspects of the problem and omit those who see the other end of the spectrum.

The ingested coin issue is a good example. I suspect that virtually all children have swallowed a coin or similar object at some time. Except for those with symptoms, probably half of the children never told their parents (I never did). Most of the parents who were told probably elected to do nothing as long as the child remained symptom free. (I elected to watch my kids when it happened.) Of the parents who sought advice, I suspect that many were told to watch for symptoms and to observe stools for the object during the next 3 to 4 days. Then, if the object did not emerge, they were told to seek medical attention to ensure that it was not still lodged in the child.

Thus, the standard for handling ingested coins and other objects appears to have been based on a selected sample of young coin swallowers whose parents were apt to seek advice. Moreover, those physicians who saw the children probably had distorted perceptions because they tended to see children with complications.

In setting up committees that set standards, we need to appreciate that "experts" may reside in both primary care and the specialties. Some of our malpractice problems relate to the establishment of standards that are too high. This also leads to defensive medicine.

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1. Fulginiti VA. Is standard practice in pediatrics 'standard'? AJDC. 1989;143:546-548.

Sir.—I consider my medical training to have been divided into three parts. The first period was the education and experience I received before medical school and residency (BMSR), the second was during medical school and residency (DMSR), and the last was after medical school and residency (AMSR). Each period provided a unique perspective, but was not complete in itself.

My medical training experience was a sheltered world where an aversion to the acute embarrassment of having the chief resident point out a flaw in my workup resulted in a compulsion to order extensive and generally uninformative batteries of tests for even the simplest of problems. It took 2 years after leaving my residency program for me to decompress from this environmentally induced paranoia.

Of course it did not surprise me that 65% of AMSR pediatricians would not order roentgenography on an asymptomatic child who had swallowed a coin. The AMSR pediatricians tell parents to watch for loose change.

Textbooks are written by academic physicians. Medical school clinic populations are generally not a representative sample of patients. Academicians see the worst of the worst or the end stage of a process, and there are some problems that they don't even get to see at all. They generally don't have the benefit of seeing the patient in the early stages of a disease and may not be around long enough to see the long-term consequences.

Textbooks based on such skewed observations are not a practical basis for the development of "universal" standards. I rarely read textbooks anymore. I am annoved by the presentation of unconnected bits of information that lack an appreciation for the pattern of the disease process. I suspect many of these texts were written by the left hemispheres of splitbrain preparations.

If, indeed, we want whole pediatric texts, then the writers need to begin to investigate the mysteries of medical life after residency and (horrors!) start learning the practical wisdom of the AMSR pediatrician. Perhaps an appropriate title for such research might be, Beyond the Hospital: Another World.

> REBECCA A. JESSEE, MD 275 Hospital Pkwy Suite 850 San Jose, CA 95119

Sir.-Allow me to comment on your observations regarding trenchant "standard practice." As a nonacademic practitioner of many years looking at the problem from the other side of the mirror, I find the following thoughts come to mind.

The crux of the problem may be that the tools used to determine standard care are designed for and function best when applied to tertiary care and may not be ideal for studying primary care situations. This could well arise partly because of the hierarchical structure of academic medicine. Most of us, especially professors, assume that a conclusion reached by a professor is probably correct. A practicing physician may not wish to differ openly with the chief of his or her service and thus may modify the primary care pattern without making an issue of it.

While we may agree that anecdotal observations are not a sound basis on which to determine a standard, perhaps consensus among physicians in primary practice should at times be considered significant and the reasons for that consensus explored. Primary care when done well has become, in fact, a specialized discipline with some strengths better represented than in a formal departmental setting.

I have lived long enough to observe that today's imperative from the medical center may be anathema 2 years hence. In addition, I could cite examples of practices that achieved consensus among practitioners years before they were accepted by the academic community as valid.

May I say in closing that I consider *AJDC* to be excellent and a great help in practice.

DAVID TOLL, MD 95 Main St St Johnsburg, VT 05819

Sir.—After reading the editorial by Fulginiti¹ and the articles by Schunk et al² and Caravati et al³ in the May issue of AJDC regarding pediatric coin ingestion, I telephoned 11 fellow pediatricians to learn how they would respond to an asymptomatic child who had swallowed a coin. I also decided to ask whether they would prescribe oral antibiotic therapy or administer an injection of benzathine penicillin to a nonallergic child weighing more than 18 kg whose throat culture results or rapid-strept test results were positive for streptococcal infection.

Atlanta, Ga, is a medical school city with two tertiary care-level children's hospitals that strongly encourage continuing medical education for their physicians. All the pediatricians I questioned are members of the "active" staffs of at least one of the children's hospitals. My questions were the same to each pediatrician: "If you have a totally asymptomatic child in no distress whose parent tells you the child has swallowed a coin, would or wouldn't you order roentgenography?" and "If you have a nonallergic child who weighs more than 18 kg and who tests positive for strept either by throat culture or rapidstrept test, would you prescribe oral antibiotic therapy or would you administer an injection of benzathine penicillin?" I didn't expect a uniformity of answers, but I was naive enough to think I would get simple yes or no answers that would fit neatly into a table.

Two pediatricians wouldn't answer

unless I told them the size of the coin. Several wanted to know the age of the child. One said the younger members of his group practice would and the older members wouldn't order roentgenography. Three physicians said they would administer benzathine injections if the child was vomiting, and two said they would leave the choice of oral or injectable therapy up to the child's parent. One physician said she thought administering benzathine to a child was "inhumane."

Of the three who said they would "always" obtain a roentgenogram, one was angry that he paid the same malpractice premiums as the eight who said they wouldn't. Two of these eight said they would obtain a roentgenogram if the coin wasn't found in the child's stool within 72 hours, and another would obtain a roentgenogram if the coin hadn't been passed after 5 days. One physician wondered if the recommendation to obtain roentgenograms was a profit-making scheme of the radiologists and emergency department physicians, and another thought it was just a "defensive medicine" ploy to keep from being sued for malpractice. Another physician wondered if the question was an "us vs them" confrontation between academic faculty in a medical school, who don't have to worry if the patient will pay the radiologist but not the pediatrician, and "us guys in the real world" who do. At first I was struck with how difficult it is to conduct a survey like Schunk et al and Caravati et al did. I spoke with 11 pediatricians for about 3 days, and these authors interviewed six times that many physicians for a period of several weeks and more than 160 families at least twice for 28 months! I was (and still am) impressed by their studies. But I wonder if any of the 65 pediatricians in Salt Lake City, Utah, wanted to know the age of the child or the size of the coin? Wouldn't some of these 65 pediatricians have obtained a roentgenogram if the child became symptomatic or failed to pass the coin in the stool after 72 hours? Tidy, informative, authoritative tables do not and cannot reflect all the factors that influence a clinician's plan of action.

The Committee on Rheumatic Fever and Infective Endocarditis of the Council on Cardiovascular Disease in the Young stated in a special report that "Failure to eradicate group A streptococci from the throat may occur more frequenty after oral antibiotic treatment than after administration of intramuscular benzathine penicillin G."4 Schwartz et al⁵ found an 18% failure rate to eradicate streptococci after 10 days of orally administered penicillin therapy (as opposed to a 31% failure rate after 7 days of therapy) despite detecting penicillinuria on days 4 and 7 of both treatment groups and on day 10 of the 10-day treatment group.

The Report of the Committee on Infectious Disease of the American Academy of Pediatrics stated in 1982 that "Relapses occur more frequently with oral penicillin G than with injected benzathine penicillin G." But 9 of the 11 pediatricians I asked said they would prescribe oral antibiotic therapy instead for an 18-kg or heavier, nonallergic child with a streptococcal throat infection, and the other 2 said they would leave the choice up

Physician	Routinely Obtain Roentgenogram — Asymptomatic Coin Ingestion	Positive — Oral Antibiotics	Strept Throat- Injectable Benzathine	
Α	Always	Yes	No	
В	No	Yes	No	
С	Depends on coin size	At parents' option		
D	Depends on coin size	Yes	If vomiting	
E	If parent requests	Yes	No	
F	No	Yes	No	
G	No	Yes, but if febrile or vomiting		
н	Yes	At parents' option		
1	No	Yes, but if vomiting		
J	If coin not passed within 5 d	Yes	Inhumane	
К	Always	Yes	No	

to the child's parent. What is the standard of care here—the vast majority of my colleagues in private practice who treat with oral antibiotic therapy or the medical school faculty who write those "special reports" and "committee statements" and advise injectable benzathine penicillin?

My attempt to tabulate my colleagues' responses appears in the Table. My own responses are not included, but I would request roentgenography for the child whenever he or she became symptomatic or didn't pass the coin within 72 hours, whichever occurs first. I treat a nonallergic child weighing more than 13.5 kg who has a streptococcal throat infection with injectable benzathine penicillin G.

However, one of my professors said, "Never say never and hardly ever say always." (He also said "watch for change in the stools.") Fulginiti in his editorial stated, "Physicians are thinking professionals and do not necessarily accept all conventional wisdom." I think that's more fortunate than not

E. NOEL PRESTON, MD Children's Medical Associates, PC 3957 Holcomb Bridge Rd, 101 Norcross, GA 30092

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Sir.—The editorial by Fulginiti about standards of practice was thoughtful and provocative. Standards of practice are of particular importance to those of us in primary care as we do want to practice high-quality medicine. Standards also have their medicolegal implications.

However, the means by which these "standards" come into being are of some importance. Dr Fulginiti correctly pointed out the central role of

experts in establishing standards and further stated that "practitioners might benefit by knowing that their practices might not conform to some standard held by experts." I would like to add that "experts" might benefit from a review of their "standards" when they do not conform to what is actually being done in primary care practice.

The problem of coin ingestion is a good case in point. Forty-five of 65 pediatricians surveyed do not automatically obtain roentgenograms of an ingested coin. I suspect they would if the child were symptomatic. The two articles that follow the editorial seem to support the viewpoints of the majority of physicians who do not conform to the "standard." The two articles presented a total of five cases of children with asymptomatic ingestion. In all of these patients, the coin passed uneventfully, and premature intervention was avoided. What is the advantage of roentgenography? We must not set standards on worst-case scenarios.

I urge caution in setting standards that are contrary to the usual way medicine is being practiced unless there is compelling evidence otherwise. At times, the "experts" may actually be those in practice with their many years of experience.

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In Reply.—I am grateful for the interest of those who responded to my editorial on standard setting in pediatric practice. I did not envision the amount of interest that my opinion would engender.

Dr Bader raises some generic and important issues. The "biases" that he speaks of are inherent in the process followed by expert committees intending to establish standards. Any committee that recognizes that its words are going to appear in court, in hospital standards, or in some other legal or semilegal context will head for a safe harbor in phrasing its recommendations. The difficulty is that data are incomplete on many issues, and yet the individual physician confronted with a single patient must decide on a course of action. Thus, the expert committee must steer between Charybdis and Scylla; Charybdis being a too cavalier recommendation, and Scylla, a too conservative one.

I am not certain that such committees always see the "worst aspects of the problem and omit those who see the other end of the spectrum." In my experience, all shades of opinion are considered, but the final "standard" reflects safety, which implies that the worst scenario is to be avoided. When applied to the coin ingestion problem, as Dr Bader does, the issue is not whether all sides of practice are considered, but what is the degree of risk that the worst side will happen, balanced by the degree of risk (and/or cost) of an effective detector of that risk (ie. the roentgenographic examination). On the other hand, Dr Bader is correct in that the sample chosen might have an intrinsic bias, ie, it does not represent all instances of coin ingestion, but only those brought to the physician's attention. If true, then the risk/benefit ratio does indeed become skewed. But that is exactly the problem that confronts the practitioner; he or she is seeing patients who are brought to medical attention, so the risk ratio can be derived from such a population.

I fully agree with Dr Bader's final point that expert committees should always have representation from the sector most likely to be affected, ie, the practicing community involved. Such members should be intelligently aggressive in that they should not be cowed or overwhelmed by the "experts."

Dr Jessee elaborates on Dr Bader's last point by asserting that practitioners (after medical school and residency) have a unique viewpoint that differs from that of their academic colleagues. However, I disagree with her assertion that all such academicians have their heads in the sands of academe. Today, most of us have had extensive patient care involvement and are much more sensitive to practice issues than was the case several decades ago. Nevertheless, I would still champion membership on expert committees (and in textbook authorship) for those individuals who can represent the practice that will be affected by the expert opinion.

Dr Toll's remarks are in agreement with those of Drs Bader and Jessee and my response applies to his comments as well. Dr Preston's attempt to determine "standards" echoes the commentary in my editorial. He found that, indeed, pediatricians are "thinking professionals" and did not simply

fall in line for the issues he queried. The comments he received reveal the degree of perception that such analytic professionals employ in "solving" a relatively straightforward clinical problem; they are not content with a formula for action but want to know the variables, presumably because such knowledge will affect their decision.

As a teacher, I am enormously gratified by such responses; mental stagnation has not set in after medical school and residency. Despite some public disclaimers, physicians attempt to do the best for their patients, even if it means that they have to go to extra lengths to reach a rational decision concerning diagnosis or treatment. On the other hand, some of the responses were mildly alarming, as they reflect the insertion of nonmedical reasons into their choices. Benzathine penicillin may hurt, but it is not necessarily an "inhumane" form of treatment for a child who needs penicillin and cannot tolerate oral medication. However, in the balance Dr Preston's little survey has more positive features than negative ones.

Dr Jones echoes that sentiment of others and adds the perspective of cost-benefit rationale in his analysis of the reports that stimulated the editorial. His letter is most pleasing in that he not only read the relevant scientific articles but interpreted them. This is the ultimate reward for authors, reviewers, and editors—an intelligent readership.

VINCENT FULGINITI, MD Editor, AJDC Tulane University School of Medicine 1430 Tulane Ave New Orleans, LA 70112

Necrotizing Granulomatosis of the Spleen in Chronic Granulomatous Disease

Sir.—Chronic granulomatous disease (CGD) is an inherited disorder of leukocyte bactericidal function that is characterized by chronic infections with widespread granulomatous lesions and recurrent abscess formation. Although recurrent abscess formation with granulomatous inflammation in multiple organs is the hallmark of this disease, review of the literature established splenic abscesses as a virtually unreported complication of CGD. We describe here splenic abscesses in a patient with CGD.

Patient Report. - A 14-year-old white boy with CGD required 17 admissions for recurrent abscesses (liver, rectum, and skin), pneumonia, osteomyelitis, and gastric outlet obstruction since 10 months of age. His disease was the X-linked type, lacking both the high- and low-molecularweight subunits of cytochrome b₅₅₈. The present admission was preceded by 3 weeks of fever and productive cough during which the patient was treated with oral amoxicillin with clavulanate potassium in addition to his regular regimen of trimethoprim with sulfamethoxazole and clindamycin hydrochloride. Despite this therapy, intermittent temperature spikes to 39°C and the productive cough persisted. At the time of admission, rhonchi and crackles were heard at the left lung base with slight dullness to percussion. No hepatosplenomegaly or adenopathy was noted. The chest roentgenogram revealed a left lower lobe infiltrate. Multiple sputum, blood, and urine cultures were negative for bacteria and fungi. The purified protein derivative (tuberculin) skin test yielded negative results, and the Mycoplasma titer was less than 1:8.

After 7 days of therapy with intravenous oxacillin sodium, ceftazidime, and oral erythromycin ethylsuccinate, increased infiltrates were seen on the chest roentgenogram. Bronchoscopy revealed neither anatomic abnormalities nor culture evidence for bacterial or fungal infection. Computed tomography (CT) showed the known pulmonary process but normal hepatic and splenic structures. A gallium scan showed only the anterior segments of the left lower lobe as a focus of infection, and an openlung biopsy yielded neither fungi nor bacteria on culture. Intravenous amphotericin B therapy was initiated at the time of the biopsy and discontinued after 7 days, when fungal cultures and stains were negative. In spite of intravenous antibiotic therapy (including oxacillin, ceftazidime, erythromycin, clindamycin, gentamicin sulfate, and trimethoprim with sulfamethoxazole in various combinations) for more than 4 weeks, the patient's temperature continued to spike to 39°C while he remained alert and appeared to be in a nontoxic condition. The antibiotic therapy was discontinued for 4 days, and rigid bronchoscopy with bronchial lavage again did not yield bacterial, viral, or fungal growth.

On day 36 of hospitalization, a second CT scan of the abdomen revealed multiple low attenuation splenic lesions varying in size, measuring up to 1 cm. In contrast, ultrasound of the spleen showed enlargement only.

When visualized during a laparotomy, the spleen was more extensively involved than anticipated and was removed. There were multiple irregular firm nodules studding the external surface ranging in size from 0.3 cm to 1.5 cm. Histologic examination showed extensive replacement of both red and white pulp by multiple confluent granulomas. These were centrally necrotized and surrounded by palisades of

histiocytes, Bacterial cultures of the surgical specimen yielded *Escherichia coli* with normal sensitivity.

After surgery there was rapid defervescence and decline of serum acute-phase reactant levels (ie, C-reactive protein and α_1 -antitrypsin), as well as a gradual decrease of the erythrocyte sedimentation rate. Postoperative antibiotic therapy included 3 weeks of intravenous amoxicillin and gentamicin followed by 3 weeks of home therapy with intravenous ceftriaxone sodium. During the entire time, he also received oral therapy with trimethoprim with sulfamethoxazole. After withdrawal of intravenous antibiotics, the patient remained well with normal sedimentation rates and acute-phase reactant levels.

Comment. - Splenic abscesses or necrotizing granulomas appear to be extremely uncommon in CGD. A literature review identified only a single publication describing abscesses in a patient with CGD.2 We have knowledge of only one other case of fatal Serratia marcescens sepsis with splenic abscesses (Paul Quie, MD, personal communication, February 1989). Our case demonstrates the development of extensive granulomatous inflammation of the spleen, complicating left lower lobe pneumonia in a patient with CGD. Computed tomography with contrast initially did not show splenic abnormalities, but a repeated study 11 days later identified some lesions. Once the spleen was directly visualized, it was clear that the CT scan underestimated the extent of splenic disease. In febrile illnesses of patients with CGD that do not yield microscopic or culture evidence of a specific pathogen, the infection most feared is aspergillosis. Therefore, diagnostic efforts are geared toward ruling out fungal infections. Aggressive, often invasive methods, such as bronchoscopy and open-lung biopsy, are necessary to obtain adequate specimens, and early treatment with antifungal agents, such as amphotericin B, is prudent while awaiting culture results.3

Continued efforts to find the cause of the fever in our patient finally allowed us to identify the uncommon source in the spleen. In patients with CGD the spleen should, therefore, be included as a possible site of infection. Management of splenic abscesses or necrotizing granulomas in CGD has not been described. In a review, 91% of patients with splenic abscesses were found to be immunocompromised because of leukemia, collagen vascular disease, disseminated malignancy,

brittle diabetes, prematurity, or chronic debilitation.4 In another study, 658 abdominal CT scans of 275 children with cancer identified 7 patients with splenic "abscesslike" lesions.5 All of them subsequently were confirmed to have fungal disease. It was, therefore, reasonable to assume that the presence of multiple well-circumscribed hepatic or splenic lesions on the abdominal CT scan of a febrile, immunosuppressed patient not responding to antibiotics and with no other source of infection is strong evidence for systemic fungal infection. Candida and Aspergillus have been found to be the major causes of the infections, and prolonged systemic antifungal therapy has been recommended. In CGD such therapy may not be appropriate. and direct visualization, culture, and, if necessary, splenectomy may be required to eradicate the infection.

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Reprint requests to Division of Allergy and Immunology, Department of Pediatrics, Washington University School of Medicine, 400 S Kingshighway Blvd, St Louis, MO 63110 (Dr Polmar). We thank Drs Paul Quie and James Keating for

critical review and kind encouragement.

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Perfumes Possibly Perilous to Pediatric Patients

Sin—The article by Scherger et al¹ in the June 1988 issue of AJDC concludes

that "asymptomatic children who ingest by history less than 105 mL of an ethanol-containing cologne, perfume, or after-shave can safely be observed at home." This recommendation is based on finding no significant toxic effects in children less than 6 years of age who by history ingested up to 105 mL of 50% to 90% ethanol. This recommendation is at best misleading and at worst dangerous. The question of whether a 12-month-old child can safely ingest 105 mL of 90% ethanol is not answered by this study. The authors quote the lethal dose of ethanol in children as 3 g/kg. Since the specific gravity of ethanol is 0.79, the lethal dose is 3.8 mL/kg of absolute ethanol. Thus, in a 10-kg, 12-month-old child, the lethal dose of a perfume containing 90% ethanol would be 42.2 mL.

Quantitation of ingested toxins by history is often difficult. However, ingestion of ethanol-containing fluids by small children must be managed based on the calculation of the maximum possible ingested dose per kilogram of body weight.

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 Scherger DL, Wruk KM, Kulig KW, Rumack BH. Ethyl alcohol (ethanol)—containing cologne, perfume, and after-shave ingestions in children. AJDC. 1988;142:630-632.

In Reply.-We appreciate the opportunity to respond to Dr Silverman's concerns. The primary conclusion of our study was that because the history of ingestion is unreliable in children, using maximum possible ingested dose of ethanol per kilogram of body weight as suggested by Dr Silverman cannot be a reliable predictor of toxicity. The children in our study who had blood ethanol concentrations measured had levels far below those predicted, and children who did not have levels measured remained asymptomatic despite having predicted levels in the extremely toxic range. Our study therefore concluded that symptoms, and not histories, should guide poison centers and clinicians in determining which children should go to a health care facility.

The concept of "lethal dose" requires clarification. No amount of ethanol ingested by a child should be a lethal dose if aggressive supportive therapy is administered in a timely

manner. Our study tried instead to determine the "toxic dose" that would require medical attention. No assertion was made that ingesting 105 mL of cologne, perfume, or after-shave (the largest amount ingested by history in our series) is nontoxic. However, even when the history indicated an ingestion this large, symptoms were unlikely. Clearly, amounts swallowed cannot be accurately determined when perfume, cologne, or after-shave exposures occur in children.

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Gastrointestinal Milk Intolerance of Infancy

Sir. - In the March 1989 issue of AJDC Berezin et al1 stated that "colonoscopy is the most effective means of establishing a definitive diagnosis" of milk intolerance of infancy. They implied a diagnosis protocol for hematochezia consisting of colonoscopy with multiple biopsy procedures, treatment with protein hydrolysate formula, and repeated colonoscopy in 2 weeks. They cautioned that "histologic findings may be similar in other disease states [but] rapid resolution and reappearance of colonic abnormalities after withdrawal and rechallenge . . . clearly establish a clinical diagnosis of protein intolerance." This would require four colonoscopies and at least two biopsies.

The cost of a colonoscopsy is about \$500, and a biopsy with pathologic diagnosis adds up to \$700. Using the protocol implied by Berezin et al, this would cost the patient between \$1200 and \$4800. This cost does not include office visits to a specialist, laboratory evaluations, or incidental costs due to

time lost by parents.

A more conservative approach would be to evaluate the infant. If no other illness is suspected and the child is in stable condition, one should proceed with removal of the milk protein from the diet, reevaluate the patient's condition in 72 hours for resolution of hematochezia, and rechallenge the infant at a future date. This would result in the cost of four office visits and four guaiac test cards at \$200. Even using the

standard of Goldman et al,2 which requires three separate challenges, the cost would not approach that of Dr

Berezin and his group.

The incidence of milk protein allergy is estimated to be around 0.5% of the infant population.3 Colonoscopy for hematachezia caused by suspected milk protein allergy would be exorbitantly expensive and probably not provide sufficient information to justify the cost.

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1. Berezin S, Schwarz SM, Glassman M, Davidian M, Newman LJ. Gastrointestinal milk intolerance of infancy. AJDC. 1989;143:361-362.

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3. Freier S, Kletter B. Milk allergy in infants and young children. Clin Pediatr. 1970;9:449-454.

Sir. – We read with interest the article by Berezin et al¹ in the March 1989 issue of AJDC wherein they reported their experience with cow's milk or soy protein-induced colitis in 22 infants. In all 19 of 22 patients who received the protein hydrolysate formula Nutramigen (Bristol-Meyers Inc, USPNG, Evansville, Ind), rectal bleeding ceased.

We describe an infant who developed symptoms of allergic colitis while receiving Nutramigen and on repeated challenge with Nutramigen but not with other hypoallergenic feeding.

Patient Report. - A 2-month-old white male with bloody diarrhea for 7 days was referred to the pediatric gastroenterology outpatient service of the Schneider Children's Hospital of the Long Island Jewish Medical Center, New Hyde Park, NY, for evaluation in April 1989. He was born without complications, the 3050-g fullterm product of a normal spontaneous vag-

inal delivery.

Initially, the infant was placed on a cow's milk formula but was changed to a soy milk formula at 3 weeks of age because of spitting up. After another week he was placed on Nutramigen due to the continuance of the spitting up. Some mild improvement was noted. Throughout this period the infant thrived, gaining weight along the 50th percentile consistently. After approximately 4 weeks into the Nutramigen feeding, his stools became loose and watery, with multiple streaks of bright red blood and mucus. The frequency of his bowel movements increased from three per day to six to seven bowel movements per day.

After 36 hours of symptoms, an abdominal flat plate, stool culture, stool Rotazyme, and urine culture were obtained, all of which were negative or within normal limits. The child was placed on an oral electrolyte solution for 24 hours and all stools ceased. The next day, half-strength Nutramigen was instituted for 24 hours and normal stools were noted. On the following day, full-strength Nutramigen was begun and bloody diarrhea returned. This persisted until our consultation 3 days later. The infant experienced no vomiting, fever, abdominal distention, or rashes. There was no intake besides the formula. The family medical history included a maternal grandmother with allergies to milk and cheeses and a maternal uncle with allergic rhinitis.

Physical Examination.-The physical examination revealed a well-developed, well-nourished infant in no acute distress. The patient's weight of 4.89 kg and height of 58 cm were both at approximately the 50th percentile for his age. The head was normocephalic and atraumatic with an open anterior fontanelle. There was no scleral icterus or oral mucosal ulceration. The neck was supple and the lungs were clear bilaterally. The heart had a regular rate and rhythm without murmurs. The abdomen was nondistended with normally active bowel sounds. It was soft and nontender with no hepatosplenomegaly or masses noted. The anal examination revealed no external fissures or fistulas. Defecation revealed loose, mucoid stool with multiple streaks of blood covering and mixed in with the stool. A rectal examination with a rigid infant proctoscope revealed an erythematous, friable lower 3 cm of the rectum without gross ulceration or polyps noted. The extremities were without cyanosis, clubbing, or edema. The skin was without hemangioma, telangiectasias, or rashes.

A complete blood cell count revealed a white blood cell count of 10.3×10^9 /L (0.69) lymphocytes, 0.24 granulocytes, and 0.07 monocytes), a hemoglobin level of 96 g/L, a hematocrit value of 0.28, and a platelet count of 277×10°/L. Stool culture results for Salmonella, Shigella, Yersinea, or Campylobacter species were again negative. A stool specimen examined for ova and parasites yielded none, but many white blood cells were noted. Pregestimil was instituted (Bristol-Meyers Inc, USPNG, Evansville Ind) and the patient was noted after 24 hours to have returned to three nonloose bowel movements per day with no blood or mucus. However, 14 days after the institution of Pregestimil, the parents reinstituted Nutramigen since they felt that the infant disliked the Pregestimil (he took 120 to 150 mL of Pregestimil per feeding compared with 180 to 240 mL of Nutramigen per feeding). Seventy-two hours after the reinstitution of Nutramigen, the bloody diarrhea returned. After 24 hours, the formula was changed to Alimentum (Ross Labs, Columbus, Ohio), another protein hydrolysate formula that the parents felt the infant took well. Again, the bloody diarrhea ceased after 24 hours. Two weeks later the infant was continuing to thrive, without any bloody diarrhea on Alimentum.

Comment. - Food sensitivity is a relatively common problem with an estimated incidence of 0.3% to 7% in infancy.2 It may present with a variety of gastrointestinal symptoms, one of which is an allergic colitis.3 Diagnosis has traditionally depended on demonstrating that the problem disappears with removal of the offending antigen and reoccurs with its reintroduction.4 The infant described herein had resolution of classic colitis symptoms with three hypoallergenic regimens (oral electrolyte solution, Pregestimil, and Alimentum). The symptoms began and returned on two (unintentional) challenges with Nutramigen, another hypoallergenic formula. Both Nutramigen and Pregestimil have the same hydrolyzed casein for their nitrogen source, although different batches might vary somewhat in their distribution of peptides. In contrast to our experience, it has been noted that some patients receiving Pregestimil experienced colitis that resolved with Nutramigen.⁵ Alimentum is another commercially available hydrolyzed casein formula. This patient's reactions suggest that there may be an antigen (modified cornstarch?) present in Nutramigen that is not present in Pregestimil, Alimentum, or the oral electrolyte solution. One should consider the possibility of intolerance to the hypoallergenic regimen when an infant with typical food-protein-induced colitis symptoms responds atypically to a casein hydrolysate formula.

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1. Berezin S. Schwarz SM, Glassman M, et al. Gastrointestinal milk intolerance of infancy. AJDC. 1989;143:361-362.

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Sir.—I read with interest the article by Berezin et al1 that appeared in the March 1989 issue of AJDC. It was commendable that the authors obtained informed consent from the legal guardian(s) of the infants before undertaking colonoscopy. It was also commendable that the protocol for the study was approved by the institutional review board for the protection of human subjects at the center involved. Another strong point of the study was the precise definition of a case of diarrhea.

The authors conclude that the presence of hematochezia is an indication for colonoscopy with videotape in infants and that the procedure is the most effective means of definitive diagnosis.

The accepted method of withdrawal and challenge is definitely more costeffective and potentially less risky than colonoscopy with videotape in infants. The issues of cost-effectiveness and morbidity were not considered by the authors before recommending the adoption of colonoscopy for diarrhea in infants.

The sample size of only 22 infants is too small to draw conclusions for milkintolerant infants. In the "Results" section it is unclear what diet the 4 infants with eosinophilia were given. Similarly, the exact diet of the 6 infants with elevated IgE levels and the 6 infants with a positive radioallergosorbent test for cow's milk was not stated; it is therefore unclear whether there were any effects due to possible interactions between multiple dietary components. Finally, the possible explanations for protection from diarrhea in the 2 infants who did not develop diarrhea following rechallenge were not addressed by the authors.

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1. Berezin S, Schwarz SM, Glassman M, Davidian M, Newman LJ. Gastrointestinal milk intolerance of infancy. AJDC. 1989;143:361-362.

In Reply. - We appreciate the pertinent and provocative comments of Dr Wenner regarding our recent article in AJDC. Indeed, we agree with several of Dr Wenner's comments. We must emphasize, however, that the purpose of this article was not to suggest that repeated colonoscopies are a cost-effective or even preferred

method of following up infants with suspected milk protein intolerance. Rather, our aim was to establish a rapid and more definitive method of diagnosis than previously available.

Our feeling is that in an infant with hematochezia and negative stool culture findings, an initial colonoscopy can identify the characteristic findings of milk-induced colitis, as stated in our article. Once a diagnosis is established, a follow-up (with a milk protein challenge) can be performed using stool hemoccult examinations rather than a formal colonoscopy. Unfortunately, this was not clear in our article.

We disagree with Dr Wenner's proposal for the diagnosis of milk-induced colitis. Hematochezia may persist for more than 72 hours after removal of the offending antigen from the diet. Under these circumstances, infants would be incorrectly diagnosed as having another cause of their rectal bleeding. In addition, hematochezia can be seen in other disorders found in an infant otherwise in stable condition (eg, lymphonodular hyperplasia1). A diagnosis of milk intolerance under these conditions would necessitate the use of an expensive hypoallergenic formula (ie, protein hydrolysate), which would not be required if a definitive diagnosis of milk-induced colitis could be ruled out.

Finally, infants with milk protein intolerance have been reported to develop life-threatening immunologic reactions when rechallenged.2,3

Therefore, we believe that in suspected cases an initial colonoscopic evaluation can be used to establish a definitive diagnosis of milk protein intolerance in a suspected population. Rechallenge with the offending protein at a later date, in association with follow-up stool hemoccult examinations, represents the most effective means of clinical follow-up.

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- 1. Kaplan B, Benson J, Rothstein F, Dahms B, Halpin. Lymphonodular hyperplasia of the colon as a pathologic finding in children with lower gastrointestinal bleeding. J Pediatr Gastroenterol Nutr. 1984;3:704-709.
- 2. Lifschitz CH, Hawkins HK, Guerra C, Byrd N. Anaphylactic shock due to cow's milk protein

hypersensitivity in a breast-fed infant. J Pediatr Gastroenterol Nutr. 1988;7:141-144.

3. Gryboski J. Gastrointestinal milk allergy in infants. Pediatrics. 1966;38:354-362.

In Reply. - Dr Pettei's case report is very interesting. Although all of our patients tolerated Nutramigen formula, the number of patients was small. Dr Pettei's case report is important in showing that milk-induced colitis may not resolve with Nutramigen, but that another hypoallergenic formula may be beneficial.

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In Reply. - Although the sample size was small, our experience indicates that colonoscopy is useful in establishing the diagnosis of milk-induced colitis. No complications were associated with colonoscopy. Repeated milk challenges, though, may initiate severe allergic reactions.1

We feel that colonoscopy should be utilized to establish the diagnosis of milk-induced colitis. Response to therapy can be monitored using stool

guaiac tests.

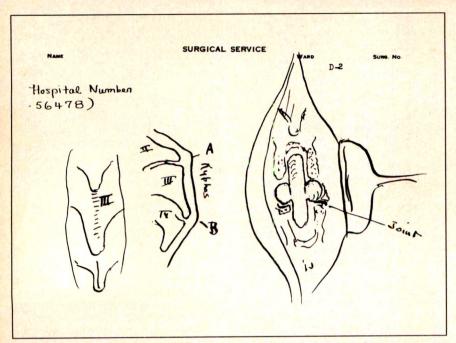
Three infants with eosinophilia were receiving a cow's milk formula and one infant with eosinophilia was receiving a soy protein formula. Four infants receiving cow's milk formula, one infant receiving soy formula, and one infant fed both formulas had an elevated IgE level. All the infants with a positive radioallergosorbent test were receiving a cow's milk formula.

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1. Gryboski JD. Gastrointestinal milk allergy in infants. Pediatrics. 1966;38:354-362.

Harvey Cushing Operates on a Child With Tuberculosis of the Spine

Sir.—We report the case of a child who presented to The Children's Hospital of Boston (Mass) in 1923 with tuberculosis of the spine and was operated on by the father of American neurosurgery, Dr Harvey Cushing.



Intraoperative view drawn by Dr Harvey Cushing following the surgery. The drawing was located above the operative note. Dr Cushing initially used pencil then covered the pencil marks with ink. A and B represent the "double knuckle" felt on the child's back preoperatively.

Patient Report.—The patient was a 6-year-old girl with a 5-year history of an increasing upper thoracic kyphosis admitted with subacute progressive paraparesis. She had a double-positive Wasserman reaction, and spine roentgenograms showed questionable "luetic" bony lesions with lateral curve to the kyphos and complete lower-extremity sensory and motor loss with active spinal reflexes. The child initially underwent treatment with the Alpine lamp and arsphenamine for presumed syphilis.

Dr Harvey Cushing was consulted as to the cause of this neurologic deficit. One week later, Cushing performed and documented the following operation in his operative sketch (Figure) and report:

At the operation... I appreciated just what it was that caused the double knuckle, A and B, that could be so clearly felt in the child's back for they represented practically the upper and lower part of the long exposed and flattened ridge-pole of the spine of the vertebrae.

After stripping off the laminae a great pad of somewhat thickened fat was disclosed showing that the canal so far as pressure was concerned was not occluded though I think it was the impression of some of the onlookers that this might have been causing the trouble. When this fatty pad was removed a thin, very hard dura and cord without fluid was exposed and on removing the laminae well away to the side two bulging nodules about the size of a pea were exposed for which at first I could not account . . .

Consequently, first on the right and then on the left side these pea-like protrusions were opened and each of them contained cheesy yellow tuberculous pus not under tension . . . Personally I cannot see that these abscesses had anything to do with the paraplegia which I believe is produced by the position of the cord stretched over the kyphos although this is ordinarily supposed not to produce paraplegia. There was certainly no evidence of any other tissue in the canal than the fatty pad which was removed from the posterior surface of the cord.

Interestingly, the perioperative pathologic diagnosis was "chronic inflammation" with "no evidence of tuberculosis." Unsatisfied with this finding, Dr Cushing injected a small fragment of the specimen into a guinea pig immediately following the operative procedure. After 6 weeks, an autopsy on the animal revealed extensive tuberculosis.

Comment.-In Cushing's era, not only was the treatment of tuberculosis less effective due to the absence of specific antimicrobial agents, but confirmation of the diagnosis itself was more difficult. In this case, the initial erroneous diagnosis of syphilis was entertained based on a positive Wassermann reaction. In 1906, August von Wassermann applied the principles of the complement fixation test method to study the serum of syphilitic patients. However, the Wassermann reaction was a nontreponemal complement fixation test. In spite of its being a great step forward at the time, some sera gave false-positive results. This was later verified when tests detecting treponemal antibodies became available.1 Lacking any hard clinical evidence for syphilis in this case, the child most likely had a false-positive Wassermann reaction.

Treatment for syphilis at that time consisted of arsphenamine. The Alpine lamp was also employed to fumigate the patient with mercury vapor. Osler² discusses the treatment in his classic textbook as follows: "The patient sits on a chair wrapped in blankets with the head exposed. The calomel is volatilized and deposited with the vapor on the patient's skin. The process lasts about twenty minutes, and the patient goes to bed wrapped in blankets without washing or drying the skin."

Cushing's talent as a medical artist is well known. He produced extensive medical illustrations, mostly of his operative cases. Following surgery, Cushing would sit and make drawings of the operative field as is seen in this case. Through sketches, he was able to convey precise information concerning the surgery for others as well as for his later reference. Mildred Codding, a medical illustrator whom he brought from The Johns Hopkins Hospital, Baltimore, Md, would often use his postoperative sketches as a guide in preparing illustrations of his cases for publication (oral communication, Mildred Codding, November 1988).

As a surgeon and clinical investigator, Cushing was thorough and honest. His operative notes are commentaries on the pathophysiologic features of the conditions he treated as well as on the surgical judgment that preceded his cases as evidenced here. His ability to find answers to scientific questions is illustrated nicely in this case. When the pathologist was not able to make the diagnosis of tuberculosis perioperatively, Dr Cushing injected part of this specimen into a guinea pig who subsequently developed the disease.

At the time this child had surgery, the inoculation of infected tuberculous material into guinea pigs was a novel diagnostic tool used only in a few European centers. In this case, as well as in others, he brought the science of the day to the bedside. This vignette, therefore, illustrates several facets of this talented surgeon who was one of the most important figures in early American neurosurgery.

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Down Syndrome and 3,3',5'-Triiodothyronine

Sir.—Since publications cross geographic but only rarely linguistic boundaries, we wish to bring to your attention our recent publication on elevated thyrotropin (TSH) levels and Down syndrome (DS).¹

Our findings are in accordance with those observed by Sharav et al.²

A prospective survey was carried out on 78 patients with DS (age range, 6 months to 16 years; mean, 9.08 ± 6.99 years) followed up at our genetics clinic, Hopital des Enfants Malades, Paris, France. The TSH levels were significantly elevated (t = 9.5; P <<<<.001) in the group with trisomy $21 (3.99 \pm 2.54 \text{ mU/L})$ as compared with 214 age-matched normal children $(2.01\pm0.85 \text{ mU/L})$. There was no difference in free thyroxine (T₄) levels between both groups (trisomy 21, 20.55 ± 3.81 pmol/L; controls, 21.12 ± 3.19 pmol/L). Free triiodothyronine (T₃) levels, however, tended to be lower in the DS group $(7.09 \pm 1.68 \text{ pmol/L})$ vs controls $(7.92 \pm 1.39 \text{ pmol/L}) (t = 2.4; P = .05).$

We observed a significant decrease in 3,3',5'- T_3 (rT₃) levels in patients with DS. The mean rT₃ value was 340 ± 147.7 pmol/L in patients with trisomy 21, whereas in 43 normal children the value was 408.56 ± 112.16 pmol/L (t=2.7; P<.01). The rT₃/TSH ratio was significantly decreased (t=5.8; P<<.001) in the DS group (118.78 ± 87.35) vs controls (253 ± 152.53). No correlations were found between age, height, or IQ and TSH, T₄, T₃, or rT₃.

Little is known about the biochemical and physiological role of rT₃. Serum reverse T₃ levels are elevated in the fetus and newborn, in hyperthyroidism, and in a variety of nonthyroid disorders.³ Elevated levels of TSH and rT₃, despite normal values of T₄ and T₃, have been reported in children treated with amiodarone hydrochloride.⁴ Low levels of serum rT₃ have been reported in hypothyroidism and in patients treated with diphenylhydantoin.⁵

We suggest that perhaps rT₃ deficiency plays a particular role in trisomy 21. Further studies are warranted to investigate the biochemical and physiological actions of rT₃ and its significance in DS.

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Kawasaki Disease Presenting With Thrombocytopenia

Sir.-Kawasaki disease may be associated with a variety of hematologic abnormalities, the most characteristic being thrombocytosis.1 Thrombocytopenia, in contrast, appears to occur rarely in children with this disease. In a recent study of 486 Japanese children with Kawasaki disease, Hara et al2 observed that 2% manifested thrombocytopenia early in their illness. To our knowledge, early thrombocytopenia has not been reported in other populations. We report the case of a child with Kawasaki disease who manifested thrombocytopenia during the first week of her illness.

Patient Report. - A 33-month-old white female child developed fever, diarrhea, and vomiting 4 days prior to admission followed 2 days later by the appearance of an erythematous eruption. On the day prior to admission, the child's pediatrician diagnosed staphylococcal or streptococcal scarlet fever and initiated treatment with dicloxacillin sodium. Throat, blood, and urine cultures obtained at this visit revealed no growth of bacterial pathogens. Due to a persistence of symptoms, the child was referred to Cleveland (Ohio) Metropolitan General Hospital.

The physical examination revealed a moderately ill-appearing child whose temperature was 38.7°C, pulse was 140 beats per minute, and blood pressure was 84/62 mm Hg. There was mild bilateral conjunctival hyperemia without discharge, erythema of the oropharynx without pharyngeal exudate, an equivocal red strawberry tongue, fissuring of the lips, and the presence of several small (diameter <1 cm) anterior cervical nodes. The skin revealed generalized macular erythema, more prominent over the face and in the perineum. A Nikolsky sign was not elicited. The extremities were normal without edema.

A white blood cell count was 13.2×109/L with 0.63 segmented neutrophils and 0.10 band neutrophils. Hemoglobin was 96 g/L; hematocrit, 0.29; platelet count, 84×10⁹/L; and erythrocyte sedimentation rate, 50 mm/hr. Urinalysis results were normal. The prothrombin time was 10.9 seconds (control, 11.4 seconds) and the activated partial thromboplastin time was 29 seconds (control, 26.3 seconds). Sodium (132 mmol/L), potassium (3.1 mmol/L), and chloride (92 mmol/L) levels were mildly depressed, while aspartate aminotransferase (60 U/L; normal, 7 to 40 U/L) and alanine aminotransferase (103 U/L; normal, 7 to 40U/L) levels were elevated. Serum blood urea nitrogen, creatinine, and total bilirubin levels were normal. Cultures of the blood, stool, and anterior nares evidenced no growth of bacterial pathogens.

The child's initial clinical findings and laboratory data suggested the diagnosis of a staphylococcal toxin-mediated process, and treatment with parenteral nafcillin sodium (150 mg/kg per day) was begun. Despite this therapy, she remained febrile and her platelet count fell to 75×109/L. On the fourth hospital day (day 8 of the illness), the child developed edema of the feet and began to experience right upper quadrant abdominal pain. While findings from an electrocardiogram and echocardiogram were both normal, abdominal ultrasonography revealed hydrops of the gallbladder. In view of these findings, a diagnosis of Kawasaki disease was made and treatment with intravenous gamma globulin (400 mg/kg per day) and aspirin (100 mg/kg per day) was initiated. In the succeeding 24 hours, the child's fever resolved, her abdominal pain improved, and she developed desquamation of the face, perineum, and subungual area of the digits. The platelet count was 562 × 10⁹/L on day 11 of the illness and reached a peak of 1220 × 109/L on day 15. A repeated echocardiogram obtained on day 12 of the illness was normal and the child was discharged home while receiving low-dose aspirin therapy (5 mg/kg per day).

Comment. - Thrombocytosis is a well-recognized finding in Kawasaki disease, usually occurring during the second week of the illness and reaching a peak of approximately 700 × 109/L during the third week. 1 Thrombocytopenia, in contrast, is a rarely reported manifestation of this disease. In the single English-language publication addressing this issue, Hara et al² observed thrombocytopenia in 10 (2%) of 486 Japanese children with Kawasaki disease. In 9 of these children, platelet counts reached a minimum of 94 ± 38 × 10⁹/L 6.8 ± 2.2 $(mean \pm SD)$ on day (mean ± SD) of the illness. The 10th patient had a persistently depressed platelet count consistent with a diagnosis of idiopathic thrombocytopenic purpura. An additional patient with idiopathic thrombocytopenic purpura as a late complication of Kawasaki disease has recently been described by Lipnick and Luban.3 The child described herein represents, to our knowledge, the first reported non-Japanese patient in whom thrombocytopenia occurred early in the course of the disease. Her platelet count reached a minimum of 75×109/L on day 6 of the illness and a maximum of 1220×10^9 /L on day 15.

The cause of early thrombocytopenia in Kawasaki disease is not understood. While speculation is hampered by the fact that bone marrow examinations were not performed in our patient or in the patients described by Hara et al,2 several possible explanations exist. In certain patients, early thrombocytopenia may be due to platelet consumption accompanying disseminated intravascular coagulation. Of the nine patients described by Hara et al,2 two had evidence of coagulation-mediated platelet consumption and seven did not have coagulation studies performed. Without further coagulation studies (eg, fibrinogen, fibrinogen-related antigens, evaluation of the peripheral smear), it is difficult to exclude a low-grade consumptive process as the cause of thrombocytopenia in our patient. Alternative explanations for early thrombocytopenia include increased platelet destruction through immune (IgG) or nonimmune (direct binding of the infectious agent to platelets) mechanisms or by suppression of megakaryocyte production by direct infection or other factors. Further studies will be required to determine not only the cause but the prevalence and severity of early thrombocytopenia in patients with Kawasaki disease.

We believe that it is highly important for clinicians to be aware that thrombo-

cytopenia may occur early in the course of Kawasaki disease. As our patient illustrates, the finding of a low platelet count must be interpreted with care as one attempts to differentiate Kawasaki disease from another process such as toxic shock syndrome in which the clinical manifestations are similiar and thrombocytopenia is commonly observed.

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Prolactinoma in a Prepubescent Girl

To the Editor.—The report by Tiwary¹ in the May 1989 issue of AJDC of a case of prolactinoma in an adolescent girl is an important addition to the literature on prolactinoma in adolescents. Many clinicians believe that these tumors occur only after pubescence has begun and endogenous estrogen is increased. The author stated that the youngest described patient of whom she is aware is a 13-year-old girl. I would like to bring to the attention of your readers a report by Chevne et al² describing a bromocriptine-unresponsive prolactin macroadenoma in a prepubescent girl, 11 years 10 months old. The symptoms actually began at age 8½ years. A trans-sphenoidal surgical excision was performed 8 months after the initiation of bromocriptine therapy. The authors recommended that a minimum 6month trial of bromocriptine therapy be used. Because of the locally invasive nature of the adenoma, radiation therapy was used as well.

Following appropriate hormonal

therapy, the patient showed an increase in linear growth and normal breast development. Androgenic response was limited to scant pubic and axillary hair.

Clinicians should be alerted to the possibility of prolactinomas in prepubescent girls as well as pubertal and

adult young women.

GEORGE D COMERCI, MD
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In Reply.—I am grateful to Dr Comerci for drawing my attention to the report by Cheyne et al. I agree with his comment "clinicians should be alerted to the possibility of prolactinomas in prepubescent girls as well as pubertal and adult young women."

CHANDRA M. TIWARY, MBBS Department of Pediatrics Brooke Army Medical Center Fort Sam Houston San Antonio, TX 78234-6200

Safe Home Use of the Compressor-Driven Nebulizer

Sir.—In his timely and informative article in the April 1989 issue of $AJDC^1$ Dr Newcomb presents a survey of the current practices of experts in the treatment of childhood asthma.

Three quarters of his experts recommended home use of nebulized medication for 5-month-old and 18-month-old patients. Abuse or overdependence on inhaled adrenergics was mentioned by eight physicians.

Our use of the compressor-driven nebulizer is similar to that of the survey respondents. We have provided this treatment to more than 200 children at home. Our patients do not undergo treatment more often than every 4 hours without calling us. Parents monitor the status of young children by observing the four signs of asthma² and checking the peak flow rate in children over 4 years of age.³ If the treatment does not produce a significant and steady improvement in signs and peak flow or the improve-

ment does not hold for 4 hours, parents will call us for an appointment or advice. Neither toxicity nor abuse has been a problem.

The major danger of administering β-adrenergic drugs at home with a compressor-driven nebulizer is not toxicity, but rather that patients will fail to seek help in a timely fashion. If the parent monitors a child's status closely, this problem can be averted. A change in signs or a fall in peak flow provides an early and clear signal that a current treatment is not effective. Usually a steroid burst is called for. In some instances, sinusitis must be treated before the asthma episode will respond properly.

THOMAS F. PLAUT, MD Asthma Consultants 125 Red Gate Lane Amherst, MA 01002

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In Reply.—Dr Plaut describes a pattern of use that places him in accord with the majority of the other experts I interviewed.

The efficacy and safety of using nebulized sympathomimetic bronchodilators at home have been addressed recently. In an inner-city pediatric population Zimo et al¹ found that emergency department visits and hospital admissions were significantly reduced after the institution of home nebulizers, especially for younger children. Their use was not associated with increased respiratory failure or other morbidity, despite probable divergence between the instructions and the actual use.

Although the use of inhaled bronchodilators obliges the physician to train parents and children in the techniques of their use and, as Dr Plaut correctly emphasizes, in monitoring the effectiveness of such treatment. the results seem to justify the effort. I am dismayed by the widespread neglect of elementary monitoring, even in children admitted to the hospital for acute, severe asthma and by the disregard for essential details of nebulizer use, such as the use of a mouthpiece even for young children with severe dyspnea. Improved education of physicians and therapists is urgently needed.

> RICHARD W. NEWCOMB, MD Pediatric Allergy and Pulmonology Service 8683 Connecticut St Merrillville, IN 46410

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In Other AMA Journals

ARCHIVES OF SURGERY

Anti-Antivivisection: Have We Waited Too Long?

Dwight E. Harken, MD, Alden H. Harken, MD (Arch Surg. 1989;124:1366-1367)

ARCHIVES OF PATHOLOGY & LABORATORY MEDICINE

Fatal Adenovirus Pneumonia in a Newborn Identified by Electron Microscopy and In Situ Hybridization

Susan L. Abbondanzo, MD; Charles K. English, MS; Elliott Kagan, MD; Richard A. McPherson, MD (*Arch Pathol Lab Med.* 1989;113:1349-1353)

ARCHIVES OF DERMATOLOGY

Norwegian Scabies in an Infant With Acquired Immunodeficiency Syndrome

Penelope Jucowics, MD; Maria E. Ramon, MD; Philip C. Don, MD, PhD; Richard K. Stone, MD; Mahrukh Bamji, MD (*Arch Dermatol.* 1989;125:1670-1671)

Acute Graft-vs-Host Disease in an Immunodeficient Newborn Possibly due to Cytomegalovirus Infection

Naji Tawfik, MB, ChB, PhD, Kowichi Jimbow, MD, PhD, FRCPC (Arch Dermatol. 1989;125:1685-1688)

Skin Nodules Over the Diaper Area

Nada A. Sweidan, MD; Salah M. Salman, MD; Abdul-Ghani Kibbi, MD; Shukrallah T. Zaynoun, MD (Arch Dermatol. 1989;125:1703)

Papular Midfacial Eruption in a Child

Aditya K. Gupta, MD; Michael T. Goldfarb, MD; James E. Rasmussen, MD (Arch Dermatol. 1989;125:1703)

Multiple Papules in a Child

Nancy A. Muffarij, MD; Mona M. Muallem, MD; Abdul-Ghani Kibbi, MD; Salah M. Salman, MD; Shukrallah T. Zaynoun, MD (Arch Dermatol. 1989;125:1703)

NEW FROM McNEIL

Ibuprofen Suspension 100 mg/5 ml

A new therapeutic alternative for fever

Antipyretic efficacy

In children with temperatures greater than 102.5°F, ibuprofen 10 mg/kg is more effective than ibuprofen 5 mg/kg or acetaminophen 10 mg/kg!

PediaProfen is indicated for the reduction of fever in children 6 months and older.

Longer duration of action than acetaminophen for fever^{1,2}

Ibuprofen 10 mg/kg provides up to 8-hour relief. That means fewer interruptions in the family's work, school, or sleep schedules.

Safety profile*

See brief summary of Prescribing Information. Significant adverse effects are reported with NSAIDs. Serious as well as minor side effects can occur with long-term use of high-dose ibuprofen. In clinical studies with over 400 pediatric patients, no significant adverse reactions were reported during short-term therapy for fever.2

Pleasant-tasting

Designed for compliance; well liked by patients in clinical studies?

References:

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Clin Pharmacol Ther. 1989;46:9-17. 2. Data on file, McNeil Consumer Products Company

From the children's fever relief specialist

McNEIL

Introducing Rc Ibuprofen Suspension 100 mg/5 ml



A new therapeutic alternative for fever

New Pedia Profen... Ibuprofen Suspension 100 mg/5 ml

The following is a brief summary only. Before prescribing, see complete prescribing information in PediaProfen labeling.

INDICATIONS AND USAGE: PediaProfen is indicated for the reduction of fever in patients aged 6 months and older, and for the relief of mild-to-moderate pain in patients aged 12 years and older.

CLINICAL PHARMACOLOGY: Controlled clinical trials comparing doses of 5 and 10 mg/kg ibuprofen and 10-15 mg/kg of acetaminophen have been conducted in children 6 months to 12 years of age with fever primarily due to viral illnesses. In these studies there were no differences between treatments in fever reduction for the first hour and maximum fever reduction occurred between 2 and 4 hours. Response after 1 hour was dependent on both the level of temperature elevation as well as the treatment. In children with baseline temperatures at or below 102.5°F both ibuprofen doses and acetaminophen were equally effective in their maximum effect. In those children with temperatures above 102.5°F, the ibuprofen 10 mg/kg dose was more effective. By 6 hours children treated with ibuprofen 5 mg/kg tended to have recurrence of fever, whereas children treated with ibuprofen 10 mg/kg still had significant fever reduction at 8 hours. In control groups treated with 10 mg/kg acetaminophen, fever reduction resembled that seen in children treated with 5 mg/kg of ibuprofen, with the exception that temperature elevation tended to return 1-2 hours earlier.

CONTRAINDICATIONS: PediaProfen should not be used in patients who have previously exhibited hypersensitivity to ibuprofen, or in individuals with all or part of the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents. Anaphylactoid reactions have occurred in such patients.

WARNINGS: Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy. Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

PRECAUTIONS: General: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints while receiving PediaProfen, the drug should be discontinued and the patient should have an ophthalmologic examination which includes central visual fields and color vision testing.

Fluid retention and edema have been reported in association with ibuprofen, therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension.

PediaProfen, like other nonsteroidal anti-inflammatory agents, can inhibit platelet aggregation, but the effect is quantitatively less and of shorter duration than that seen with aspirin. Ibuprofen has been shown to prolong bleeding time (but within the normal range), in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying

hemostatic defects. PediaProfen should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients on PediaProfen should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

In order to avoid exacerbation of disease of adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ibuprofen is added to the treatment program.

The antipyretic and anti-inflammatory activity of PediaProfen may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Since ibuprofen is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation. Prospective studies on the safety of ibuprofen in patients with chronic renal failure have not been conducted.

Safety and efficacy of PediaProfen in children below the age of 6 months has not been established.

Pregnancy: Reproductive studies conducted in rats and rabbits at doses somewhat less than the maximal clinical dose did not demonstrate evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. As there are no adequate and well-controlled studies in pregnant women, this drug should be used during pregnancy only if clearly needed. Because of the known effects of nonsteroidal antiinflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during late pregnancy should be avoided. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats. Administration of PediaProfen is not recommended during pregnancy

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with ibuprofen is gastrointestinal. In controlled clinical trials, the percentage of adult patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

Adverse reactions occurring in 3% to 9% of patients treated with ibuprofen: nausea, epigastric pain, heartburn, dizziness, rash. Adverse reactions occurring in 1% to 3% of patients: diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract, headache, nervousness, pruritus, tinnitus, decreased appetite, edema, fluid retention (generally responds promptly to drug discontinuation). Still other reactions (less than 1 in 100) have been reported, and are detailed in the full summary of prescribing information.

DOSAGE AND ADMINISTRATION: Shake well prior to administration.

Fever Reduction in Children 6 months to 12 years of age: Dosage should be adjusted on the basis of the initial temperature level (See CLINICAL PHARMACOLOGY for a description of the controlled clinical trial results). The recommended dose is 5 mg/kg if the baseline temperature is less than 102.5°F or 10 mg/kg if the baseline temperature is greater than 102.5°F. The duration of fever reduction is generally 6-8 hours and is longer with the higher dose. The recommended maximum daily dose is 40 mg/kg.

Mild to moderate pain: 400 mg every 4 to 6 hours as necessary for the relief of pain in adults.

In controlled analgesic clinical trials, doses of ibuprofen greater than 400 mg were no more effective than 400 mg dose.

HOW SUPPLIED: PediaProfen Ibuprofen Suspension 100 mg/5 ml (teaspoon)

orange, berry-vanilla flavored

Bottles of 4 oz (120 ml)......NDC 0045-0469-04 Bottles of 16 oz (480 ml)......NDC 0045-0469-16

SHAKE WELL BEFORE USING. Store at room temperature. Caution: Federal law prohibits dispensing without prescription.

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Our special appreciation is extended to each person on this list for his or her efforts on behalf of our readers, authors, and editorial staff.—ED.

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Leads From the MMWR

Morbidity and Mortality Report Centers for Disease Control, Atlanta

Surveillance for Epidemics—United States

MMWR. 1989;38:694-696

ALTHOUGH STATE health departments document investigations of disease epidemics and outbreaks, there is no national system for surveillance of epidemics. In 1988, a 5-month pilot project to assess the feasibility and utility of a standard computerized surveillance system for epidemics was conducted by state epidemiology programs in Maryland, New York, Oklahoma, and Washington, and by the Epidemiology Program Office, CDC.

From June through October, 1988, the four participating state epidemiology offices used a uniform data collection system to record reported epidemics investigated by their staffs or by other agencies in their states. For this project, an epidemic or outbreak was defined as: "A recent or sudden excess of cases of a specific disease or clinical syndrome. For a foodborne outbreak, 'n' greater than or equal to 2; for other outbreaks, 'n' greater than or equal to 3." Although designed principally to collect information on epidemics, the system also allowed for reporting other epidemiologically important events, including individual cases of rare diseases (e.g., botulism and human rabies) and toxic exposures without documented subsequent illness (e.g., a hazardous material spill during transport).

During the 5 months, 116 events were reported. Maryland and Oklahoma, which already maintained systems of epidemic reporting similar to the pilot system, accounted for 39 (34%) and 33 (28%) reports, respectively. Washington and New York, with pre-existing systems considerably different from the pilot system, accounted for 25 (22%) and 19 (16%), respectively. The number of reported events per 100,000 population was 1.0 in Oklahoma, 0.8 in Maryland, 0.5 in Washington, and 0.1 in New York.1 Local health departments originated reports for 69 (59%) events. The timeliness of reporting was measured as the interval between date of onset for the index case and date of report to the state health department. Dates were recorded for 106 events; of these, the reporting interval was less than or equal to 1 week for 64 (60%) and less than or equal to 2 weeks for 78 (74%).

Seventy-nine (68%) of the events were epidemics or outbreaks; of these, 77 (97%) were caused by communicable diseases. The majority of these were relatively small outbreaks-51 (66%) involved fewer than 10 persons. The largest, an outbreak of viral gastroenteritis, involved 64 persons at a nursing home in Oklahoma. The most frequently reported locations associated with outbreaks were commercial food establishments (25%), nursing homes or other long-term care facilities (15%), and the general community (10%). For the 39 (51%) infectious disease outbreaks in which an etiologic agent was reported, the most common agents were Salmonella (26%) and hepatitis A virus (23%).

Reported by: C Groves, E Israel, MD, State Epidemiologist, Maryland State Dept of Health and Mental Hygiene. S Kondracki, DL Morse, MD, State Epidemiologist, New York State Dept of Health. P Archer, S McNabb, GR Istre, MD, State Epidemiologist, Oklahoma State Dept of Health. M Chadden, JM Kobayashi, MD, State Epidemiologist, Washington State Dept of Social and Health Svcs. Council of State and Territorial Epidemiologists. Div of Field Svcs, Epidemiology Program Office, CDC (MMWR Vol. 38, No. 40).

CDC Editorial Note: The current national system of notifiable disease reporting (data reported weekly in MMWR tables) provides surveillance data on a wide range of diseases, many of which can cause epidemics. The 121city mortality surveillance system (data reported weekly in MMWR) is used to assist in identifying epidemic influenza.2 However, except for a limited set of problems (e.g., waterborne outbreaks3), no uniform national system of surveillance exists for epidemics. Consequently, neither CDC nor state epidemiology programs have access to uniform, comparable surveillance data for monitoring temporal and geographic trends of epidemics or for providing national estimates of the frequency of epidemics.

Although most states maintain written records for epidemic surveillance, many do not routinely computerize these data. Increased use of automation might facilitate analysis and evaluation of such data, as well as expedite intervention/prevention efforts. Systematic surveillance of epidemics could be used to improve disease prevention efforts at both state and national levels. For example, epidemic surveillance data could be used to evaluate and improve regulations and standards of public health practice related to child-care licensing, restaurant inspections, and environmental hazard control. This approach might permit comparison of the effectiveness of differing standards in different local or state jurisdictions, measurement of the impact of changes in standards over time, and early detection of changing patterns in the transmission of notifiable diseases, such as the recent increased incidence of hepatitis A transmission among drug abusers.4

This pilot project demonstrated both the feasibility and constraints associated with development of a standard system for surveillance of epidemies. Each of the participating states recognized the utility of the data generated by the project. However, two of the states noted that a permanent system would require substantial revision of their current procedures for collecting and reporting surveillance data. The wide variability of the ratio of reported events to population size probably reflects differences in data included in this system rather than in occurrence of epidemics (e.g., most reports of small foodborne disease outbreaks in New York come directly to the State Bureau of Community Sanitation and Food Protection rather than to the office of the state epidemiologist).

At its annual meeting in May 1989, the Council of State and Territorial Epidemiologists unanimously passed a resolution supporting the concept of state-based epidemic surveillance and endorsed CDC efforts to develop a uniform system that permits comparable information to be collected, analyzed, and shared among the states.

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National Adult Immunization Awareness Week

MMWR. 1989;38:708-710

NATIONAL ADULT IMMUNIZATION Awareness Week emphasizes the importance of appropriately immunizing all adults against eight diseases: diphtheria, hepatitis B, influenza, measles, mumps, pneumococcal disease, rubella, and tetanus. Immunization programs have markedly reduced the incidence of vaccine-preventable diseases in children, but many adults remain susceptible because they are inadequately immunized.

National Adult Immunization Awareness Week (October 22-28) highlighted collaborative efforts by federal, state, and local health agencies, public health organizations, and professional, private, volunteer, and other organizations to improve adult immunization. These efforts have included the following:

In June 1988, greater than 40 health organizations formed the National Coalition for Adult Immunization (NCAI). NCAI's major goals include increasing public- and private-sector collaboration and involvement in improving the immunization status of adults through information and education programs for providers and consumers.

In October 1988, the Health Care Financing Administration (HCFA) collaborated with CDC in providing resources for nine demonstration projects. Conducted by state, county, and city health departments and one university medical center, these projects will determine whether Medicare payment for influenza immunization increases vaccine coverage and reduces morbidity, mortality, and demand for health-care services. The projects

were initiated in 1988, and all will be completed by 1992.

In 1988, the State of Hawaii Department of Health, assisted by HCFA and CDC, implemented a Pneumococcal Disease Initiative. The initiative included evaluation of the incidence of pneumococcal bacteremia and mortality in Hawaii; surveys of immunization knowledge, attitudes, and practices among Hawaii physicians and older residents; and a statewide vaccination program for Medicare beneficiaries. From September 1, 1988, through February 23, 1989, community-based mobile clinics administered pneumococcal vaccine to 15,909 elderly residents. Concurrent with the initiative, vaccine sales in the private sector indicated that vaccine use more than doubled.

In 1987, CDC entered into a 3-year cooperative agreement with the American Managed Care and Review Association to assist health maintenance organizations (HMOs) in developing adult immunization policies and practices. The agreement involves activities to determine HMO policies and procedures, immunization coverage, and disease impact and to develop intervention strategies. Six HMOs, representing greater than 50,000 enrollees, are participating.

Reported by: Div of Immunization, Center for Prevention Svcs, CDC (MMWR Vol. 38, No. 41).

CDC Editorial Note: Each year, adults develop vaccine-preventable diseases because they have not received the recommended vaccines. 1-7 For example, in each of several recent epidemics, greater than 40,000 influenza-related excess deaths occurred. 3.8 Approximately 40,000

deaths related to pneumococcal infections and an estimated 300,000 new hepatitis B cases occur annually. Among young adults, the incidence of measles and mumps has increased. 4.9 Ten percent to 15% of childbearingaged women are not immune to rubella, and most Americans greater than 60 years of age lack adequate protection against tetanus and diphtheria. Safe and effective vaccines are available for all these diseases, and the cost of vaccination is substantially less than the cost of treating the disease.

Improving vaccine use among adults requires a multifaceted strategy involving collaboration of health-care providers, consumer groups, and public and private organizations. National Adult Immunization Awareness Week draws attention to efforts that promote prevention and control of vaccine-preventable diseases.

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The Editorial Board Speaks . . .

Vincent A. Fulginiti, MD





Dr Fulginiti has been editor of AJDC since January 1983. During that interval, much change has occurred—the topic of his contribution below. The journal has undergone a facelift in format, significant change in content, and now reaches every pediatrician and resident in pediatrics in the files of the American Medical Association. New features have been added and the editorial staff seeks to have each issue contain something for everyone in the field of pediatric health care provision, research, and education. The journal has moved from a content of largely clinical reports to a variety of articles ranging from laboratory and animal research, to well-structured clinical studies, astute clinical observations, and ethical, legal, and societal issues. The editorial board hopes that the journal now reflects the discipline that it addresses with substantial articles that affect every phase of our activities. We hope that we continue to serve our readers in this effort and echo the changes in pediatrics.

CHANGE AND RESPONSE TO CHANGE

Societal change swirls about us. We are reeling under current events, both those that affect society at large and medicine in particular. Just a few years ago, it would have been unthinkable to envision a Berlin Wall that was crumbling under the pressure of hundreds of thousands of East Germans who now pass freely through its gates. In the same time frame, medicine has seen obstetricians leave their practices in the United States, because of the risk, cost, and torment of potential malpractice actions. How many of us would have predicted that Colombia would go to "war" with the drug barons and turn the country into a bloody area in the interest of stemming drug abuse? Which of us would have predicted that a major congressional thrust might result in a change in physician reimbursement that equates payment with effort, irrespective of a procedural component?

These mixed examples cannot be equated in terms of the impact on the world, but they all illustrate that change is inevitable, and the only predictability in our lives is that change will occur. From the time the first bipeds walked the earth, humans have attempted to change the relationships of one individual to another, of one group of individuals to another group, to alter the environment, and to develop ways to fend off harmful elements in that environment. Our capacity to think, make judgments, solve problems, and simply answer questions posed by the world about us, irrespective of the usefulness of the answers, has always resulted in change. Why, then, are we continually surprised by change? Why do we seem unprepared to accept the inevitable? Why do we resist such change until forced to accept it, since it will happen, whether we accept it or not?

I am not a philosopher and cannot give weighty explanations for human behavior over the eons. I have been an observer of the medical milieu for more than 30 years now and can offer the observation that, as a discipline and as individuals, we fail to predict the inevitable, and respond to it with resistance. Witness the changes in medical practice in the past three decades. We have gone from solo practice and neighborhood hospitals to a complex system involving group practices, health maintenance organizations, preferred provider organizations, referral hospitals that provide care at some distance from our homes, and complex health care arrangements that continually expand the definition of the "system." At each step, we have failed to predict that practice

would change, and have resisted incorporation of the new methods until we were forced to do so by reality. I remember my professors telling us in medical school that group practice was an evil that would destroy medicine as it was then known. It has not destroyed practice; rather, the changes have reflected advances in medical methods and changes in our lifestyle wants and needs. We have been late in adjusting to such change, and often, others in society have dictated the shape and nature of the evolved systems.

Medical education has also undergone change, and educators have traditionally resisted such alterations. Even today we find individuals and whole faculties resistant to the needed alterations in curriculum design, teaching methods, content, and sites for clinical education. And yet, we know that change will occur; history tells us that it will happen and a few pioneers among us lead the way, but are resisted at each step.

With such historical imperatives and lessons, why do we continue to resist changes in medicine, medical practice, medical education, and medical thought? Some might claim that innovation is not necessarily "good," and that the "old" ways are best... after all, are they not "tried and true"? We have heard these explanations voiced for each change contemplated. We revel in blaming others for attempting to alter an "excellent" system, be it in the practice or in the educational arena. Some resist change because it is uncomfortable; habit dies hard and provides a safe haven that is predictable and nondisturbing. Change implies relearning, an alteration in procedure, a new conceptual framework, and effort in all of these. Nevertheless, change generally implies improvement, and the effort is usually worthwhile.

The following are among today's burning issues for society and medicine: the inadequacy of access to medical care for many of our citizens; the high cost of medical care for all of us; the lack of physicians in rural areas and inner cities; and the lack of minority students, practitioners, and faculty. Little foresight or imagination is needed to recognize that society will attempt to "solve" these problems. Will physicians sit on the sidelines and bewail the efforts of sociologists, economists, legislators, and others? Or will we roll up our mental and physical sleeves and take action, participate, and have a vital role in designing the solutions? The correct response seems obvious . . . but will we do it?

Skin Testing Prior to Measles Vaccination for Egg-Sensitive Patients

The recrudescence of measles and the recommended reimmunization of older children¹ spotlights the problem of measles vaccination for the eggsensitive patient. Measles vaccine (and mumps vaccine) is grown in chick embryo cell culture (not embryonated eggs), so there is a very low, but detectable, presence of egg-related antigens in the vaccine. In this issue

See also p 33.

of the AJDC, Dr Andrew Kemp and associates² from Sydney, Australia, suggest that despite a history of immediate hypersensitivity reactions to egg protein, measles vaccine can be given safely without performing a vaccine skin test.³ Kemp et al make his recommendation based on the following facts:

- 1. They immunized 32 children with a history of egg sensitivity without performing skin tests and observed no adverse reactions.
- 2. A certain percentage of allergic children (5% to 10%) will react to the vaccine skin test (particularly children with eczema); most of these children can receive measles vaccine safely.^{4,5}
- 3. Some children who react to measles vaccine will not react to skin testing; these children have non-IgEmediated anaphylactoid reactions.⁵

I strongly disagree with the conclusions of Kemp et al. I believe skin testing is always indicated prior to measles vaccination in subjects with proved or suspected egg allergy associated with immediate reactions (ie, hives, swelling of the mouth or throat, respiratory difficulty, hypotension, shock, etc).

Herman et al⁶ identified IgE antibodies to ovalbumin in two children who developed urticaria, angioedema, and respiratory difficulty following measles vaccine. They also found that six other subjects with systemic reactions to ovalbumin had IgE antimeasles vaccine antibodies (by radioimmunoassay) and positive skin test reactions to measles vaccine. Such IgE-mediated reactions are admittedly unusual; this rarity explains why Kemp et al could immunize 32 consecutive children without a reaction if such reactions occur in 1 in 100 chances or less.

The American Academy of Pediatrics Committee on Infectious Disease (Red Book Committee)3 recommends that skin testing with diluted vaccine be done for any person who has had an anaphylactic reaction following egg ingestion (hypotension, urticaria, shock. wheezing, laryngospasm, swelling of mouth or throat, etc). Persons allergic to eggs who only develop rash, abdominal pain, or other delayed manifestations need not be skin tested. The testing should be done by personnel familiar with the treatment of anaphylaxis and with adrenalin immediately available.

The Red Book Committee³ recommends diluting vaccine in saline (1:10) and performing a scratch, prick, or puncture test, using histamine and saline as positive and negative controls, respectively. If the test result is negative after 15 to 20 minutes, intradermal testing (0.02 mL of 1:100 dilution) is done, again using saline and histamine controls. If this is negative, repeated intradermal testing is done at a 1:10 dilution. If this third test result is also negative, the vaccine is then administered in a setting where treatment of anaphylaxis is immediately available. Many busy practitioners may want to refer the patient to an allergist for this three-step, ninetest injection procedure, especially if he or she is not familiar with skin testing procedures or management of anaphylaxis.

Greenberg and Birx⁷ have suggested a shortened skin test procedure consisting of a single intradermal test using a 1:100 dilution of mumps-measles-rubella vaccine, based on testing 15 egg-sensitive children, all of whom had positive skin test reactions to eggs. The vaccine skin test results were negative and mumps-measles-rubella vaccine was given successfully in all cases. I have also used this method with good results.

Patients who have a positive skin test reaction to the vaccine can be given a series of graded injections, ie, they can be "desensitized." A schedule is provided in the *Red Book*. Again anaphylaxis should be anticipated and adrenalin should be available.

As Kemp et al document, these precautions are unnecessary most of the time. However, for the rare patient with proved egg sensitivity, skin testing is a bothersome but prudent procedure, permitting all the children to receive vaccine safely. It will also vaccinate the physician from the plaintiffs lawyer, who will surely ask, "Why didn't you do the recommended skin test?"

> E. RICHARD STIEHM, MD Division of Immunology Department of Pediatrics UCLA School of Medicine Los Angeles, CA 90024

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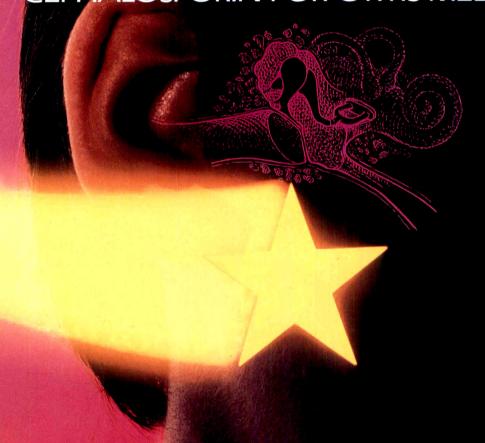
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*Due to susceptible organisms. Please consult **Clinical Studies** section of brief summary for limitations on usage Results of clinical trials in infections due to *Haemophilus influenzae, Branhamella catamhalis, Streptococcus pyogenes,* and *Streptococcus pneumoniae*. Tablets should not be substituted for suspension in otitis media.

Please see brief summary of Prescribing Information on last page.

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*Due to susceptible organisms, Haemophilus influenzae and Streptococcus pneumoniae.

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SUPRAX* cefixime/Lederle BRIEF SUMMARY. Please see package insert for full Prescribing Information INDICATIONS AND USAGE

Ottis Media caused by Haemophilus influenzae (beta-lactamase positive and negative strains), Moraxella (Branhamella) catarrhalis (most of which are beta-lactamase positive), and Streptococcus ovogenes.*

Note: For information on otitis media caused by Streptococcus pneumoniae, see CLINICAL STUDIES section.

Acute Bronchitis and Acute Exacerbations of Chronic Bronchitis caused by *S pneumoniae and H influenzae* (beta-lactamase positive and negative strains).

Perform culture and susceptibility studies to determine causative organism and its susceptibility to

SUPRAX. Therapy may begin while waiting for study results and may be adjusted when results are

Pharyngitis and Tonsillitis caused by S pyogenes

Note: Penicillin is the usual drug of choice in the treatment of *S pyogenes* infections, including the prophylaxis of rheumatic fever. SUPRAX is generally effective in the eradication of *S pyogenes* from the nasopharynx, however, data establishing the efficacy of SUPRAX in the subsequent prevention of rheumatic fever are not available.

Uncomplicated Urinary Tract Infections caused by Escherichia coli and Proteus mirabilis* Efficacy for this organism was studied in fewer than ten patients with otitis media.

CLINICAL STUDIES

In clinical trials of otitis media in nearly 400 children between the ages of 6 months and 10 years, Spneumoniae was isolated from 47% of the patients, Hinfluenzae from 34%, B catairhalis from 15%, and *S pyogenes* from 4%

The overall response rate of *S pneumoniae* to cefixime was approximately 10% lower and that of Hinfluenzae or B catarrhalis approximately 7% higher (12% when beta-lactamase positive strains of Hinfluenzae are included) than the response rates of these organisms to the active control drugs. In these studies, patients were randomized and treated with either cefixime at dose regimens of

in these studies, patients were randomized and treated with either cefixime at dose regimens of 4 mg/kg bid or 8 mg/kg qd, or with a standard antibiotic regimen. Sixty-nine to 70% of the patients in each group had resolution of signs and symptoms of otitis media when evaluated two to four weeks posttreatment, but persistent effusion was found in 15% of the patients. When evaluated at the completion of therapy, 17% of patients receiving cefixime and 14% of patients receiving effective comparative drugs [18% including those patients who had *H influenzae* resistant to the control drug and who received the control antibiotic) were considered to be treatment failures. By the two-to four-week follow-up, a total of 30% to 31% of patients had evidence of either treatment failure or recurrent disease.

Bacteriological Outcome of Otitis Media at Two- to Four-Weeks Posttherapy Based on Repeat Middle Ear Fluid Culture or Extrapolation from Clinical Outcome

Organism	Cefixime ^(a) 4 mg/kg bid	Cefixime ^(a) 8 mg/kg qd	Control ^(a) drugs
Streptococcus pneumoniae	48/70 (69%)	18/22 (82%)	82/100 (82%)
Haemophilus influenzae beta-lactamase negative	24/34 [71%]	13/17 (76%)	23/34 (68%)
Haemophilus influenzae beta-lactamase positive	17/22 (77%)	9/12 (75%)	1/1(b)
Moraxella (Branhamella) catarrhalis	26/31 (84%)	5/5	18/24 (75%)
Streptococcus pyogenes	5/5	3/3	6/7
All Isolates	120/162 (74%)	48/59 (81%)	130/166 (78%)

An additional 20 beta-lactamase positive strains of *H influenzae* were isolated, but were excluded from this analysis because they were resistant to the control antibiotic. In 19 of the the clinical course could be assessed, and a favorable outcome occurred in 10. When these cases are included in the overall bacteriological evaluation of therapy with the control drugs, 140/185 [76%] of pathogens were considered to be eradicated.

Tablets should not be substituted for suspension when treating otitis media.

CONTRAINDICATIONS

Known allergy to cephalosporins. WARNINGS

BEFORE THERAPY WITH SUPRAX IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO SUPRAX OCCURS, DISCONTINUE THE DRUG. SERIOUS, ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, CORTICOSTEROIDS, PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Administer cautiously to allergic patients.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by Clostridium difficile is a primary cause of severe antibiotic-associated diarrhea including pseudomembranous colitis. Pseudomembranous colitis has been reported with the use of SUPRAX and other broad-spectrum antibiotic lincluding paracrolides, semisynthetic penicillins, and cephalosporins). It is important to consider this diagnosis in patients who develop diarrhea in association with antibiotic use. Symptoms of pseudomembranous colitis may occur during or after antibiotic treatment and may range in seventy from mild to life threatening. Mild cases usually respond to drug discontinuation alone. Moderate-to-severe cases should be managed with fluid, electrolyte, and protein supplementation. When the colitis is not relieved by drug discontinuance, or when it is severe, oral vancomycin is the drug of sociated pseudomembranous colitis produced by C difficile. Other causes of colitis should be excluded.

General: Prolonged use may result in overgrowth of nonsusceptible organisms. If superinfection

occurs, take appropriate measures.

Carefully monitor patients on dialysis. Adjust dosage of SUPRAX (cefixime) in patients with renal ontinuous ambulatory peritoneal dialysis and hemodialysis (See DOSAGE AND ADMINISTRATION.)

Prescribe cautiously in patients with a history of gastrointestinal disease, particularly colitis. **Drug Interactions:** No significant drug interactions have been reported to date. **Drug/Laboratory Test Interactions:** A false-positive reaction for ketones in the urine may occur with tests using nitroprusside but not with those using nitroferricyanide.

SUPRAX administration may result in a false-positive reaction for glucose in the urine using Clin-itest**, Benedict's solution, or Fehling's solution. Use glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix*** or Tes-Tape***) A false-positive direct Coombs test has been reported during treatment with other cephalosporin

antibiotics, therefore, it should be recognized that a positive Coombs test may be due to the drug. Carcinogenesis, Mutagenesis, Impairment of Fertility: Although no lifetime animal studies have been conducted to evaluate carcinogenic potential, no mutagenic potential of SUPRAX was found in standard laboratory tests. Reproductive studies revealed no fertility impairment in rats at doses up to 125 times the adult therapeutic dose.

Usage in Pregnancy: Pregnancy Category B: Reproduction studies have been performed in mice and rats at doses up to 400 times the human dose and have revealed no evidence of harm to the fetus due to SUPRAX.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during preg-nancy only if clearly needed.

Labor and Delivery: SUPRAX has not been studied for use during labor and delivery. Treatment should only be given if clearly needed.

Nursing Mothers: It is not known whether SUPRAX is excreted in human milk. Consider discontin-uing nursing temporarily during treatment with this drug.

Pediatric Use: Safety and effectiveness of SUPRAX in children aged less than 6 months have not been established.

The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in pedi-ric patients receiving the suspension, was comparable to adult patients receiving tablets.

ADVERSE REACTIONS

Most adverse reactions observed in clinical trials were of a mild and transient nature. Less than four percent (4%) of patients in the US trials discontinued therapy because of drug-related adverse reac-tions. Commonly seen adverse reactions in US trials of the tablet formulation were gastrointestinal events, which were reported in 30% of adult patients on either the bid or the qd regimen. Clinically mild gastrointestinal side effects occurred in 20% of all patients, moderate events occurred in 9% of all patients, and severe adverse reactions occurred in 2% of all patients, individual event rates included diarrhea 16%, loose or frequent stools 6%, abdominal pain 3%, nausea 7%, dyspepsia 3%, and flatulence 3%. The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in pediatric patients receiving the suspension was comparable to adult patients receiving tablets

Symptoms usually responded to symptomatic therapy or ceased when SUPRAX was discontinued.

Several patients developed severe diarrhea and/or documented pseudomembranous colitis, and a few required hospitalization

The following adverse reactions have been reported following the use of SUPRAX. Incidence tates were less than 1 in 50 liess than 2% except as noted above for gastrointestinal events. Gastrointestinal: Diarrhea, loose stools, abdominal pain, dyspepsia, nausea, and vomiting. Several cases of documented pseudomembranous collits were identified during the studies. The onset

of pseudomembranous colitis symptoms may occur during or after therapy. **Hypersensitivity Reactions:** Skin rashes, urticaria, drug fever, and pruritus

Hepatic: Transient elevations in SGPT, SGOT, and alkaline phosphatase Renal: Transient elevations in BUN or creatinine.
Central Nervous System: Headaches 3%; dizziness.

Hemic and Lymphatic Systems: Transient thrombocytopenia, leukopenia, and eosinophilia. Pro-

gation in prothrombin time was seen rarely

Other: Genital prunitus, vaginitis, candidiasis.

The following adverse reactions and altered laboratory tests have been reported for

cephalosporin-class antibiotics:

Adverse Reactions: Allergic reactions including anaphylaxis, Stevens-Johnson syndrome, ery thema multiforme, toxic epidermal necrolysis, superinfection, renal dysfunction, toxic nephropathy, hepatic dysfunction, including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with nal impairment when the dosage was not reduced (see DOSAGE AND ADMINISTRATION and OVERDOSAGE). If seizures associated with drug therapy occur, discontinue drug. Administer anticonvulsant therapy if clinically indicated.

Abnormal Laboratory Tests: Positive direct Coombs test, elevated bilirubin, elevated LDH, pancy-

openia, agranulocytosis

OVERDOSAGE

Gastric lavage may be indicated; otherwise, no specific antidote exists. Cefixime is not removed in significant quantities from the circulation by hemodialysis or peritoneal dialysis. Adverse reactions in small numbers of healthy adult volunteers receiving single doses up to 2 g of SUPRAX did not differ from the profile seen in patients treated at the recommended doses.

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Measles Immunization in Children With Clinical Reactions to Egg Protein

Andrew Kemp, MBBS, PhD, FRACP; Peter Van Asperen, MDBS, FRACP; Anne Mukhi, SRN

 Thirty-five egg-sensitive children who received measles immunization without adverse sequelae are described. Thirty-two of the children had a history of immediate hypersensitivity reactions to egg protein, including 22 who developed a generalized reaction after oral exposure to egg. There were also 3 highly allergic children, with immediate hypersensitivity reactions to other food, who, despite having never been exposed to egg, developed large skin prick test wheals to egg white. Measles vaccine was given to all children without prior vaccine skin testing. There were no adverse reactions. It is suggested that measles vaccine can be given to children with a history of generalized or localized urticaria/angioedema on exposure to egg protein without prior skin testing.

(AJDC. 1990;144:33-35)

There is continuing controversy concerning measles immunization in children who are allergic to egg proteins. The package insert with the vaccine states that hypersensitivity to egg protein is a contraindication to immunization. Kamin et al^{1,2} have presented a total of 22 cases of clinical egg sensitivity in children in whom measles immunization was given without problems. A subsequent report has described two

For editorial comment see p 32.

children with allergic reactions to egg protein who developed generalized immediate reactions after the administration of measles vaccine. This has led to the recommendation that skin testing with vaccine should be performed in egg-sensitive children prior to administration of the vaccine. 4 In this study we

report a further 35 cases of egg-sensitive children in whom measles vaccine was administered without problems.

SUBJECTS AND METHODS

Children were seen during a 5-year period from 1983 to 1988. There were 23 boys and 12 girls. Thirty-two children had a history of immediate sensitivity reactions to egg protein. Three children had developed immediate hypersensitivity reactions to milk and as a result had never ingested egg protein. However, all 3 of these children had a large (>8 mm) wheal on skin prick testing to egg white.

Clinical reactions to egg in all cases occurred within 1 hour of ingestion or exposure to egg and were classified into the following three grades: grade 1, immediate symptoms of urticaria/angioedema and erythema, localized to the face; grade 2, generalized immediate symptoms of urticaria/angioedema and erythema, and/or immediate onset of vomiting; and grade 3, generalized immediate symptoms of urticaria/angioedema and erythema plus respiratory symptoms of wheeze and/or stridor.

At the time of presentation for immunization all children were avoiding egg protein. Skin prick tests were performed with egg, albumen, and egg yolk (Hollister Stier, Washington, DC). The size of the reaction in millimeters was expressed as the mean of the maximum diameter and its perpendicular to the nearest 0.5 mm.

Measles vaccine prepared from attenuated Schwartz strain of virus (Rimevax, Smith Kline & French, Rixensart, Belgium) (n = 2), or measles/mumps vaccine prepared from Enders attenuated Edmonston strain of measles (M-M-Vax, Merck Sharp & Dohme, West Point, Pa) (n = 33), were given as a single dose in the casualty department of the Children's Hospital, Camperdown, Sydney, and children were observed for 1 hour prior to discharge. Both vaccines are prepared in chick embryo cell cultures. Skin testing with the vaccine was not performed.

RESULTS

The clinical features of the children are summarized in the Table. Ten of the

children had grade 1 reactions and 22 had grade 2 or 3 reactions while 3 had never ingested egg protein. Eighteen of the 35 children also had clinical immediate hypersensitivity reactions to milk protein and 6 had clinical immediate hypersensitivity reactions after ingestion of peanut products.

On skin prick testing 34 children reacted to egg albumen with a mean wheal size of 6.5 mm and one 14-month-old infant who had her most recent immediate reaction to egg 6 weeks prior to her measles immunization was not skin tested. Twenty-seven children were also skin tested with egg yolk and 26 reacted with the mean wheal size being 4.6 mm. Overall, the mean age of administration of measles vaccine was 24.9 months (range, 11 to 101 months) and the mean age of skin prick test with egg white was 25.1 months (range, 5 to 95 months).

Three children aged 54 months, 19 months, and 21 months had never been exposed to egg. The first two children were brothers with anhidrotic ectodermal dysplasia, a condition known to be associated with immediate food hypersensitivity reactions. 5 All three children suffered from severe atopic dermatitis, and had a history of immediate food hypersensitivity reactions to milk and other foods. The 54-month-old boy developed an anaphylactic reaction to the inadvertent administration of milk in mashed potato at the hospital, and required epinephrine hydrochloride and oxygen therapy. These three children, despite never having been given egg to eat, had large skin prick wheals 8.5, 8.5, and 9 mm to egg white.

Three children had anaphylactic reactions after environmental exposure to egg albumen powder. Two of these reactions occurred 4 years and 1 year after measles immunization was given and the third, 2 months prior to measles

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Clinical Features					
Reaction	No. of Children	Mean (Median) Age at 1st Reaction, mo	Mean (Median) Age at Measles Immunization, mo	Mean (Median) Age at Egg Skin Prick Test, mo	Mean Egg Albumen Prick Test Wheal Size, mm
Grade 1	10	10.6 (6)	16.8 (14)	15.8 (14)	5.9
Grade 2	18	8.3 (7)	28.9 (18)	31.7 (19)	6.4
Grade 3	4	7.8	22.5	15.5	6.0

immunization. Another four children had a history of immediate reactions to egg that had occurred on either inadvertent exposure or deliberate challenge after the measles immunization and one child had clinical egg sensitivity documented by a formal in-hospital egg challenge after measles immunization. Thus seven of the children exhibited egg sensitivity after the measles vaccine had been administered.

COMMENT

This study describes 32 children with immediate food hypersensitivity reactions to egg protein and a further 3 markedly atopic children with positive skin prick test results who had never been exposed to egg protein. In all children immunization was given with no adverse reactions. In the present study, 80% (28/35) of patients who were given measles vaccine were less than 2 years of age as compared with the patients of Kamin et al1,2 of whom 27% (6/22) were less than 2 years of age at the time of measles immunization. Clinical egg hypersensitivity reactions can be transient with spontaneous resolution around 3 to 5 years of age associated with disappearance or a marked decrease in size of the skin prick test result in about half the cases.7 Larger wheal sizes (>3 mm) are associated with subjects with clinical sensitivity.8 Thus, the size of wheals and presence of skin prick test positivity at the time of immunization, plus the age of children indicate continuing sensitivity to egg protein at the time of immunization. In addition sensitivity to egg was demonstrated in seven of the children by clinical reactions occurring following exposure to egg protein at a time after their measles vaccination.

There are a number of highly eggsensitive children in the present report. Four of the children had generalized symptoms of either wheezing or laryngeal edema in their initial reaction. Three other children developed an anaphylactic reaction in the same room where powdered egg white was being handled without any direct physical contact. Another 8-year-old girl had been followed up by us from birth as part of a prospective study. Although her first exposure to egg had produced only a grade 2 reaction, subsequent exposures had been associated with severe wheezing and at the age of 8 years, just 4 months prior to administration of measles vaccine, she had developed a severe generalized urticarial reaction with marked vomiting and wheezing from the inadvertent exposure to a fresh salad that had been contaminated with a minute amount of egg protein.

Egg sensitivity appears to be quite common in the community. In a prospective study of infants with a family history of atopy, 6% (5/78) developed a clinical immediate hypersensitivity reaction to egg in the first 20 months of life.8 The overall incidence of clinical egg sensitivity in a large (500) cohort of atopic children was 5.6%.9 Despite this high frequency of egg sensitivity and the fact that many millions of doses of measles vaccine have been administered over the years, to our knowledge there is not a single reported case of fatality due to an immediate reaction to measles vaccine. In the years 1979 to 1982 the deaths temporally associated with measles vaccine administration in the United States were examined. There were six deaths with a rate of 0.7 deaths per million doses of vaccine. None of these could be related to an acute anaphylactic reaction. 10

Despite the fact that the measles vaccine is grown in chicken fibroblast cells, the manufacturers have continued to list egg hypersensitivity as a contraindication to measles immunization. The description of clinical egg sensitivity in patients in whom measles immunization

produced no reaction and the lack of reports of significant adverse immediate reactions to measles vaccine led to attempts to have the contraindication of egg allergy removed from the package inserts to measles vaccine.11 Subsequently the report of two children allergic to egg who developed a generalized reaction to measles vaccine⁸ led to the recommendation that a complicated series of three skin tests be performed prior to the vaccine administration in egg-sensitive children.4 A simpler regimen has subsequently been suggested.12 Egg sensitivity was defined as the inability to eat an egg without anaphylactic symptoms such as hypotension, urticaria, shock, wheezing, laryngospasm, or swelling of the mouth or throat.4 Thus, localized or generalized urticaria and swelling of the lips would qualify under this definition. If the result of skin prick test to the vaccine is positive a desensitization procedure giving graded doses of vaccine over a number of hours is recommended. These recommendations are based on two reports of immediate reactions to measles vaccine in presumed egg-sensitive children. However, there are many more reported cases (at least 28)13-16 of immediate reactions to measles vaccine unrelated to egg sensitivity. It is not totally excluded that one or both of the reported cases of Herman et al3 were not of the latter type. Furthermore, one of the two reported reactions would not have been prevented by current recommendations as this child had suffered an idiopathic anaphylactic reaction unassociated with a known egg sensitivity or administration of egg protein.3

As we have not performed vaccine skin tests we cannot comment on the likelihood of subjects who show a positive reaction to the vaccine. A problem with vaccine skin testing is the observation that a significant proportion of subjects may react. Thus, Juntunen-Back-

man et al16 found that 7% of 134 children with symptoms of atopic disease (asthma, eczema, cow's milk or egg allergy) reacted on skin prick testing to measles/ mumps vaccine. Interestingly, 4 children referred because of acute immediate reactions following measles immunization were all skin prick testnegative to the vaccine. In addition 2 children who were positive on skin testing with the vaccine received vaccine and developed no complications. Aukrust et al13 described 6 children with immediate reactions to measles/mumps vaccine who did not react to skin prick testing. It would therefore appear that skin prick testing positivity to measles vaccine may be reasonably common and these children will not necessarily react to the vaccine, while the great majority of children with reactions of an immediate nature to measles/mumps vaccine will not be identified by a positive skin

prick test. Furthermore there is no clear proof that the graded dose regimen of immunization recommended would prevent the very rare anaphylactic type reactions to measles vaccination.

The present series of 35 cases and previously published evidence1,2,12 totaling 37 cases indicate that any reaction at all to measles/mumps vaccine is unlikely in children with clinical immediate hypersensitivity reactions to egg protein. Furthermore, the great majority of published cases of immediate reactions to measles vaccine are not related to clinical egg sensitivity and would not have been prevented by the policy of immediate hypersensitivity skin prick testing in those children who are known to be egg sensitive. In light of these findings we suggest that a reasonable policy is to immunize children with a history of immediate hypersensitivity

reactions to egg protein in an area of a hospital, such as an emergency department, where any allergic reaction can be treated if it occurs. If there is a history of local or generalized urticaria, and/or angioedema alone, measles immunization can be given without prior skin testing. Children who have developed hypotension, stridor, and wheezing after exposure to egg protein or have required resuscitation with oxygen and epinephrine from an allergic reaction to egg protein could be considered for skin testing, although the role of skin testing is unproved in the prevention of acute reactions to measles immunization. It should also be explained to the parents that immediate anaphylactic type reactions to measles vaccine have been described unrelated to egg sensitivity.

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Longitudinal Changes in the Bone Mineral Content of Term and Premature Infants

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· With the use of photon absorptiometry, bone mineralization was measured at birth and 8 and 16 weeks after delivery in 12 very-low-birth-weight premature (mean \pm SD gestational age, 31 \pm 1.5 weeks) infants who required minimal medical support. Simultaneously, 19 healthy term infants were studied. Throughout the study, each neonate received modified 84-kJ/30 mL formula containing no added calciferol. The recommended daily allowance (400 IU) of calciferol was given to each infant as an oral supplement. Serum 25-hydroxyvitamin D, calcium, phosphorus, and parathyroid hormone concentrations were monitored biweekly and were normal. Bone mineral content and bone width significantly differed at birth between the term and premature infants. However, by 16 weeks after delivery, the premature infants had exceeded the bone mineral status of the term infants at birth, and their bone mineral content was not significantly lower than that of the term infants. These data indicate improved bone mineralization as compared with previously reported data from very-low-birth-weight neonates.

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Rickets of prematurity or osteopenia is a well-recognized disorder of bone mineralization among very-low-birth-weight (VLBW) neonates, particularly those with chronic illness that requires extended and complex medical therapy. Currently, its cause is thought to be multifactorial, with a deficiency in calci-

um and phosphorus intake representing a major causative factor. Several groups of investigators have hypothesized that premature neonates with minimal illness who received no parenteral nutrition would demonstrate improved bone mineralization compared with VLBW neonates who required more extensive medical support. To test this hypothesis, a longitudinal assessment of bone mineralization in VLBW neonates who required only minimal medical support was undertaken.

PATIENTS AND METHODS

Thirty-one study neonates, 19 term and 12 premature infants, were enrolled in the study within 24 hours of birth. Women with a history of a normal term pregnancy were chosen at random from those delivering at the Medical University of South Carolina, Charleston, between January 1986 and March 1988. Mothers of premature infants delivered during the same period were also contacted at random after the presence of minimal lung disease was clinically established in their infant. The investigation was approved by the University Human Research Committee, and written parental consent was obtained for each newborn before the study began.

Neonatal gestational age was initially determined from the history of the mother's last menstrual period and was confirmed with a Dubowitz examination within 36 hours of birth. Weight for both term and prematurely delivered infants was determined biweekly with a standard balance scale.

The premature infants were generally fed via orogastric tube supplemented with intravenous glucose water during the first 2 weeks of life; otherwise all infants were fed by nipple. No infant received parenteral fluid containing amino acids, calcium, or phosphate salts or lipid. Although the exact daily volume of formula intake per kilogram of

body weight was not measured for each neonate throughout the entire 16-week study, for the hospitalized premature infants, oral intake until discharge from the hospital was recorded and used to derive mineral intakes from manufacturer's data sheets.

To facilitate a consistent daily intake of calciferol, each neonate received throughout the study a modified 84-kJ/30 mL formula that contained 0.51 g/L of calcium, 0.39 g/L of phosphorus, and no added calciferol. The recommended daily allowance (400 IU) of calciferol was then given to each infant in a glycerol carrier as a daily oral supplement. Since compliance with calciferol dosage is difficult to document after discharge from the hospital, serum 25-hydroxyvitamin D concentrations were monitored biweekly. These 25-hydroxyvitamin D determinations were performed as previously described.9 Serum calcium and phosphorus levels as well as parathyroid hormone (PTH) concentrations were measured biweekly throughout the study. 10-12 Normal adult values (range) for PTH and 25-hydroxyvitamin D using these assays in our laboratory are 0.29 to 0.85 ng/mL and 25 to 125 nmol/L, respectively. Because of volume requirements for laboratory assessment, the serum ionized calcium concentration was measured only in term infants, and the total serum calcium level was measured in premature infants. Normal adult values for ionized calcium using the assay in our laboratory are 1.20 to 1.30 mmol/L. Phosphorus concentrations using the assay in our laboratory are consistent with values previously reported for neo-

Bone mineral content (BMC) and bone width (BW) were measured with the photon absorptiometric system (Lunar Radiation, Inc, Madison, Wis), in which a collimated, 3-mm-diameter photon beam from a low-activity (radioactive iodine 125) source was passed beneath the distal third of the right radius. The site of bone mineral assessment was at the junction of the middle and distal thirds of the radius. This region of the radius has the least variation in mineral content,

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thus minimizing error generated by measuring slightly different bone sites throughout a longitudinal study. Measurements of BMC and BW were made within the first 2 days of life and subsequently at 8 and 16 weeks of age. Reproducibility (without repositioning the arm) for the five scans performed for each determination of BMC and BW was reflected by a mean ±SD coefficient of variation of $1.1\pm0.7\%$ and $0.8\pm0.5\%$, respectively. The "repositioning error" determined by repeating measurements of BMC and BW after repositioning the arm is small. The correlation coefficients between measurements before and after repositioning of the arm were .99 for both BMC and BW.

Infant weights and gestational ages were correlated with the bone mineralization determinations. Furthermore, figures demonstrating BMC and BW changes from 29 to 58 weeks after conception were constructed from the birth values obtained from all 31 study infants plus the 8- and 16-week values from only the 19 full-term infants. A sigmoidal model was selected consistent with normal neonatal growth. Specifically, the data were fitted by a cubic polynomial using leastsquares error estimation procedure. The 95% confidence intervals were established about the predicted polynomial to provide normal 95% upper and lower limits for BMC and BW. The 8- and 16-week mineralization values from the 12 premature infants were not used in developing these limits as these data may not reflect "normal" bone changes. They were, however, fit by a second cubic polynomial and plotted with the birth values for comparison with the limits for normal mineralization.

All data were analyzed using analysis of variance methods with repeated measures on individual patients. These analyses were followed by standard Student's t tests for independent groups with Bonferroni adjust-

ments for multiple comparisons. Pearson correlation coefficients were used to determine the association of variables. Curvilinear and linear regression lines relating the dependent variables, BMC and BW, to the independent variable, weeks after conception, were calculated. The best fit was determined by R^2 values for the specific model used. Confidence intervals were calculated using the predicted values from the model ± 1 SD.

RESULTS

The study patients included 1 term and 1 premature white infant and 18 term and 11 premature black infants. Seven of the term and 5 of the premature infants were male. Of the 12 premature infants, 3 were electively delivered secondary to maternal preeclampsia, and 9 were delivered after the spontaneous but premature rupture of the amniotic membranes. The mean (±SD) gestational age for the term and premature study infants was 39.8 ± 1.1 weeks and 31.0 ± 1.5 weeks, respectively. Similarly, the mean $(\pm SD)$ birth weight for these infants was 3416 ± 363 g and 1281 ± 177 g, respectively. All infants were of appropriate size for their gestational age¹⁵ and free of congenital abnormalities. Furthermore, their postnatal growth was consistent with reported normal values.¹⁶

All infants were at or above birth weight and were being solely enterally fed 420 kJ/kg or more daily by 2 weeks of age. The mean daily calcium and phosphorus intakes per kilogram of body weight for the hospitalized premature infants are shown in Table 1. The biweekly serum calcium, phosphorus, and PTH concentrations for all infants throughout the entire study are shown in Table 2. Although the phosphorus concentrations were significantly (P<.05) greater in the term than in the premature neonates after the age of 2 weeks, the concentrations in both the term and premature neonates were within the normal range throughout the 16-week study. The biweekly weights for both the prematurely delivered and term infants are shown on Table 3.

None of the study infants required major medical support, such as ventilator therapy or parenteral nutrition, and

	Week					
Mineral	1 (n = 12)	2 (n = 12)	3 (n = 12)	4 (n=9)	5 (n=9)	6 (n=6)
Calcium,	33+12	80+13	88 + 15	80+0	01+8	94±7
mg/kg per day Phosphorus, mg/kg per day	33±12 25±9	80±13 61±10	88±15 67±12	89±9 68±7	91±8 70±6	94 = 72 =

*Values represent mean ± SD. Numbers of infants decreased over time as infants were discharged from the hospital.

		Term Infants			Premature Infants	1
Week	PTH, ng/mL	Calcium, mmol/L	Phosphorus, mmol/L	PTH, ng/mL	Calcium, mmol/L	Phosphorus, mmol/L
0	0.36 ± 0.36	1.42±0.18	1.90 ± 0.50	0.65 ± 0.14	2.18 ± 0.22	1.85 ± 0.50
2	0.78 ± 0.38	1.18 ± 0.14	2.60 ± 0.65	0.77 ± 0.20	2.22 ± 0.28	2.30 ± 0.25
4	0.78 ± 0.24	1.34 ± 0.18	2.75 ± 0.50	0.71 ± 0.35	2.28 ± 0.18	2.20 ± 0.20
6	0.65 ± 0.19	1.32 ± 0.18	2.90 ± 0.50	0.72 ± 0.31	2.30 ± 0.28	2.15 ± 0.20
8	0.62 ± 0.18	1.38 ± 0.14	2.85 ± 0.50	0.63 ± 0.13	2.32 ± 0.28	1.90 ± 0.20
10	0.56 ± 0.14	1.38 ± 0.18	2.60 ± 0.45	0.60 ± 0.26	2.22 ± 0.22	1.90 ± 0.25
12	0.57 ± 0.20	1.32 ± 0.12	2.35 ± 0.40	0.60 ± 0.17	2.40 ± 0.12	2.00 ± 0.20
14	0.59 ± 0.19	1.32 ± 0.12	2.45 ± 0.35	0.60 ± 0.17	2.38 ± 0.20	2.00 ± 0.15
16	0.59 ± 0.28	1.32 ± 0.10	2.40 ± 0.60	0.43 ± 0.14	2.40 ± 0.14	1.90 ± 0.15

^{*}Values represent mean ± SD. Calcium values for term neonates represent ionized concentrations, and calcium values for premature neonates represent total values.

none had sepsis or intraventricular hemorrhage. Similarly, none of the premature infants studied had neonatal asphyxia, respiratory distress syndrome, or a blood pH level documented as less than 7.3. Each premature neonate initially required an incubator for warmth. Three and 12 premature infants, respectively, experienced apnea (none requiring therapy) and/or transient oxygen therapy (<40% for <48 hours). None of the 31 study infants was treated with diuretics, theophylline, or any other medication known to affect calcium metabolism.

Longitudinal bone mineralization data from both the term and premature infants are shown in Tables 4 and 5. In both groups, the BMC and BW significantly (P<.001) increased during the first 4 months of life as determined by analysis of variance. Although the BMC values were significantly (P<.001) different between the term and preterm infants at birth, by 16 weeks after delivery, there was no longer a significant difference between the two groups. Interestingly, when the data were ana-

CONTRACTOR OF THE PARTY OF THE	Table 3.—Weight Gain in Term and Premature Neonates*				
Age, wk		Premature Infants (n = 12)			
0	3379 ± 400	1281 ± 177			
2	3688 ± 492	1315 ± 204			
4	4424 ± 270	1787 ± 682			
6	4853 ± 486	2264 ± 746			
8	5246 ± 565	2919 ± 678			
10	5751 ± 654	3376 ± 729			
12	6341 ± 574	3807 ± 724			
14	6553 ± 788	4133 ± 550			
16	7021 ± 845	4587 ± 550			

^{*}Values represent mean \pm SD in grams.

Table 4.—Bone Mineral Content (BMC) in Term and Premature Infants During the First 16 Weeks of Life*			
	BMC, g/cm		
Age, wk	Term Infants	Premature Infants	
0	0.091 ± 0.02	0.056 ± 0.01	
	(n = 19)	(n = 12)	
8	0.100 ± 0.01	0.058 ± 0.01	
	(n = 19)	(n=11)	
16	0.119 ± 0.02	0.099 ± 0.04	
	(n = 17)	(n=10)	

^{*}Values represent mean ± SD. Numbers of infants decreased over time as infants were discharged from the hospital.

lyzed using analysis of covariance controlling for birth weight, the BMC of term and premature infants at birth and 8 and 16 weeks was not significantly different. Although the BW was significantly (P < .001) different at birth between term and preterm infants, it was not significantly different at 8 or 16 weeks of age.

At birth, the BMC measurements for the 31 neonates were significantly (P<.001) correlated with gestational age. Similarly, the BMC measurements were significantly (P < .04) correlated with weight in both study groups at birth and 8 weeks.

The BW measures at birth were also significantly (P<.001) correlated with gestational age in the 31 study neonates. The BW was significantly (P<.04) correlated with weight at birth in the preterm infants and at 16 weeks (P < .05) in both term and preterm infants.

Bone mineral content and BW were significantly (P<.001) correlated with each other at birth in both term and premature infants but not at 16 weeks. Figures 1 and 2 demonstrate the change in BMC and BW, respectively, of the 12 premature infants after delivery and allow visual comparison with the variation in bone mineralization measured in all 31 study neonates at birth and in the term infants at 8 and 16 weeks after delivery.

Finally, Table 6 summarizes the 25-hydroxyvitamin D concentrations measured at birth, 8, and 16 weeks in the term and preterm infants. (Although biweekly measures were obtained, only birth and 8-week and 16-week values are shown.) The concentrations at birth and at 8 weeks but not at 16 weeks were significantly (P<.05) greater in the premature infants than in the term infants.

Serum specimens from one term infant were spilled during analysis, and in one term infant and two premature infants, the 16-week specimen was not obtained. A question also arose regarding the validity of one BMC value ob-

and Pre	Table 5.—Bone Width (BW) in Term and Premature Infants During the First 16 Weeks of Life*			
	BW, cm			
Age, wk	Term Infants	Premature Infants		
0	0.474±0.10 (n=19)	0.387±0.06 (n=12)		
8	0.499 ± 0.05 (n = 19)	0.496 ± 0.10 (n = 11)		
16	0.616 ± 0.07 (n = 17)	0.643±0.11 (n=10)		

*Values represent mean ± SD. Numbers of infants decreased over time as infants were discharged from the hospital.

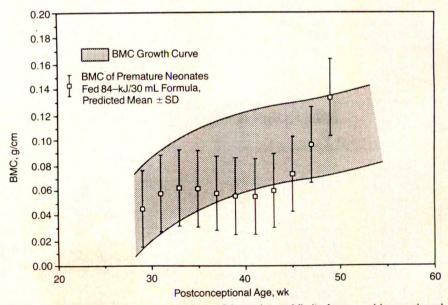


Fig 1.-Estimated upper and lower 95% confidence interval limits for normal bone mineral content determined from observations after 29- to 42-week observed values of term infants. The mean (\pm SD) predicted bone mineral content (BMC) for preterm infants is superimposed.

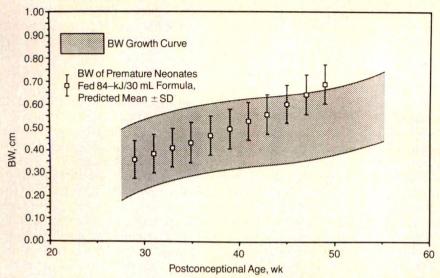


Fig 2.—Estimated upper and lower 95% confidence interval limits for normal bone width (BW) determined from observations after 29 to 42 weeks of gestation plus the 8- and 16-week observed values of term infants. The mean $(\pm SD)$ predicted BW for preterm infants is superimposed.

Table 6.—Longitudinal Assessment of the 25-Hydroxyvitamin D Status of Term and Premature Neonates*				
		vitamin D Level, nmol/L		
Age, wk	Term Infants (n = 18)	Premature Infants (n = 12)		
0†	20±15	35±5		
8†	50 ± 25	115±30		
	60 ± 30	150 ± 160		

*Values represent mean ± SD.

†At birth and 8 weeks of age, premature concentrations were significantly greater than term, P < .05.
‡At 16 weeks, there were only 17 term and 10 premature infant values.

served in a prematurely delivered infant at 49 weeks after conception. Although the observation argues for the proposed model and suggested conclusion that BMC for premature and term infants converges with continued extrauterine growth, this observation was considered an outlier for these analyses. The mean (\pm SD) BMC at 49 weeks after conception for the premature neonates with the outlier included was 0.099 ± 0.04 g/cm and without the outlier was 0.086 ± 0.01 g/cm. The difference between these two values is not significant (t=.89, P<.40).

COMMENT

Previous reports using photon absorptiometry have produced intrauterine values for both BMC and BW. 4.17

These values are similar to those measured in our present study. Furthermore, longitudinal assessments of bone mineralization (taken at varying neonatal ages after delivery) have been reported in neonates. 2.6,18-20 Much of these previous data, as in this study, were derived from infants with minimal disease. However, the results of these earlier studies are quite different from those of the current study. Therefore, the values generated in this study represent unique observations.

With the data collected at birth, an intrauterine curve of bone mineralization (for both BMC and BW) throughout the last trimester of gestation was constructed (Figs 1 and 2). Interestingly, the BMCs of the premature infants in this study at the postconceptional age of 45 weeks were the same as those of term infants at birth; this similarity suggests that the two groups mineralized their bones in a similar fashion after conception even though the prematurely delivered infants had a shorter period of intrauterine existence.

Bone width in the premature infants progressed more rapidly than BMC, as previously observed. The BW also increased more rapidly in premature than in term infants such that, at 16 weeks after delivery, the mean BW of the premature infants actually exceeded that of the term infants at the same age after delivery, even though the premature

infants were at a lower postconceptional age. This observation implies that the premature neonates were developing bone matrix much more rapidly than their full-term counterparts, but the reason(s) for this is unclear. The normal serum PTH level as well as the normal serum calcium and phosphorus concentrations in these premature infants indicate an adequate calcium and phosphorus status.

In an important earlier longitudinal study of BMC and BW in VLBW preterm infants, a striking deviation from the intrauterine bone mineralization curve was observed. In that study, the calcium and phosphorus intakes of the neonates were low. This low mineral intake was postulated to be a major cause for the delayed bone mineralization observed. Moreover, the direct association between decreased dietary calcium and phosphorus intake and delayed neonatal bone mineralization has been consistently observed. 19,20,22

In two additional earlier longitudinal studies, Greer and McCormick5,18 observed that VLBW infants with bronchopulmonary dysplasia were no more likely to develop osteopenia than a comparable group of VLBW infants without bronchopulmonary dysplasia. Moreover, since neonates in these studies, both with and without bronchopulmonary dysplasia, were extremely immature, had prolonged and complicated hospitalizations, and had inadequate intakes of calcium and phosphorus, it was concluded that several factors in addition to decreased mineral intake and other than chronic lung disease may have caused their delayed bone mineralization. Interestingly, although unexplained, both of these studies demonstrated a relatively decreased BMC and BW among the study neonates and simultaneously an increasing skeletal growth (length). These data have also been confirmed in subsequent investigation.3

Furthermore, a recent report of aluminum loading in premature infants receiving parenteral nutrition²³ and the known association of osteomalacia with aluminum loading in animal studies²⁴ may potentially describe an additional causative factor for neonatal osteopenia. On the other hand, all formulafed infants as well as those who receive

parenteral nutrition solutions simultaneously receive an aluminum load, and the relation between dietary aluminum loading in neonates and bone mineralization is not clear. 25-27

The premature infants in this study were primarily black (11 of 12). Although no racial differences in neonatal bone mineralization have been described, the improved mineralization noted in this study suggests such a possibility. Black adults have been reported to have more dense bones than white adults. ²⁸ In a report by Steichen et al, ²⁹ neonatal bone mineralization was noted not to be different at birth between black and white infants, but no longitudinal racial assessment has been described.

The 25-hydroxyvitamin D concentrations noted in Table 6 indicate that the values at birth and 8 weeks for the premature infants were significantly (P<.05) greater than those for term infants. Since cord-blood levels of 25-hydroxyvitamin D in both term and premature newborns have been reported to be significantly correlated with maternal concentrations, this observation may reflect a difference in the maternal

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25-hydroxyvitamin D status of these two groups of neonates. These observations may also be related to a lack of compliance in giving the daily calciferol dose to the term infants. More likely, however, they reflect the fact that the preterm neonates were of lower body weight than the term infants. Thus, while receiving similar daily amounts of calciferol, the premature infants were actually receiving more calciferol per kilogram per day than the term infants.

Finally, the most striking observation in this study was the degree of bone mineralization documented in premature infants being solely enterally fed an 84-kJ/30 mL formula. The calcium and phosphorus intake for these infants while hospitalized was appreciably lower than the previously reported 120 to 130 mg/kg per day and the 70 to 80 mg/kg per day calcium and phosphorus requirement for an intrauterine rate of mineralization between 32 and 36 weeks of gestation.20,30 Nevertheless, the BMC and BW in these premature neonates increased steadily throughout the study period, consistent with the intrauterine rate demonstrated in Figs 1 and 2.

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The failure to find a difference in either the BMC or BW between term and preterm infants at 16 weeks after delivery could be the result of a type II statistical error. The power (27% for BMC and 12% for BW) is low secondary to the small sample size. On the other hand, this observation may be related to the absence of extreme prematurity and/or to a prolonged and complicated hospitalization among these infants.

These data demonstrate bone mineralization values for 12 premature neonates as well as a cohort of 19 term infants over the first 4 months of life. All of these infants were enterally fed with a modified 84–kJ/30 mL formula, received sufficient amounts of calciferol, calcium, and phosphorus, and had normal serum PTH levels. A more rapid rate of bone mineralization was observed among these premature neonates than has been previously reported from similar infants requiring more extensive medical support.

This study was supported in part by grant HD-22542 from the National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Md. Ross Laboratories, Columbus, Ohio, produced the 84-kJ/30 mL formula without added calcitriol.

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Comparison of Acellular and Whole-Cell Pertussis-Component DTP Vaccines

A Multicenter Double-blind Study in 4- to 6-Year-Old Children

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 An acellular pertussis-component combined diphtheria and tetanus toxoids, and pertussis (APDT) vaccine adsorbed was compared with a licensed whole-cell pertussis-component combined diphtheria and tetanus toxoids, and pertussis (DTP) vaccine adsorbed for reactogenicity and immunogenicity when given as the fifth DTP immunization to eighty-two 4- to 6-year-old children. The reaction rates with both vaccines were low; APDT vaccine recipients had significantly less pain and warmth at the injection site than did DTP vaccine recipients. Antibody responses to pertussis antigens (lymphocytosis-promoting factor, filamentous hemagglutinin, and agglutinogens) and to diphtheria and tetanus toxoids were all brisk. The APDT vaccine recipients had a more marked response in antibodies to filamentous hemagglutinin and a less marked response in agglutinins than whole-cell vaccine recipients. On the day after immunization, both APDT and DTP vaccine recipients had an increase in mean leukocyte and neutrophil counts. This APDT vaccine is immunogenic and less reactogenic than a DTP vaccine with a whole-cell pertussis component when administered as a booster to 4- to 6-year-old children.

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The licensed combined diphtheria and tetanus toxoids, and pertussis

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Reprint requests to Department of Pediatrics, UCLA School of Medicine, Los Angeles, CA 90024-1752 (Dr Cherry). (DTP) vaccines adsorbed have been successful in reducing pertussis morbidity and mortality in the United States. However, the vaccines have been associated with a high rate of local and systemic reactions. Therefore, a new vaccine of equal or greater efficacy but less reactogenic is desirable and has become a top priority of the newly formed National Vaccine Advisory Committee.

In Japan, six acellular pertussis-component DTP (APDT) vaccines have been developed and used for routine immunization of children aged 2 years and older since the fall of 1981. ^{3,4} In general, these vaccines produce minimal side effects; currently, their use is controlling epidemic pertussis in Japan.

One Japanese APDT vaccine manufactured by Takeda Chemical Industries, Osaka, Japan, was formulated into an APDT vaccine with diphtheria and tetanus toxoids prepared by Wyeth Laboratories, Philadelphia, Pa, and underwent limited testing in the United States. 5-10 More recently, the Takeda acellular pertussis component has been formulated by Lederle Biologicals, Pearl River, NY, into another APDT vaccine that contains Lederle diphtheria and tetanus toxoids. In this article, we report the results of a doubleblind study comparing the Lederle-Takeda APDT vaccine with Lederle DTP vaccine when it is given as the fifth DTP immunization to 4- to 6-year-old children.

SUBJECTS AND METHODS Subjects

Eighty-three healthy 4- to 6-year-old children were enrolled at three study sites. One DTP vaccine recipient received her fourth dose of DTP vaccine at 9 months of age and was excluded from the analysis. All of the

other children had received four prior immunizing doses of DTP vaccine at the regularly scheduled intervals in the first 2 years of life. Informed consent was obtained from the parents after the design and purpose of the study were explained.

Forty-one children received APDT vaccine, and 42 children received DTP vaccine in a randomized double-blind fashion. The children were seen at days 0, 1, and 30, and 1 year later. At the initial visit, each child received 0.5 mL of vaccine administered into the deltoid muscle. The parents maintained a diary of local and systemic reactions for 10 days after immunization. Oral temperature was recorded 3, 6, 24, 48, and 72 hours after immunization. The presence or absence of the following reactions was recorded at 3 and 6 hours after vaccination and daily thereafter for 10 days: local pain, erythema, induration, and swelling; site temperature; drowsiness; irritability; anorexia; and vomiting. At the first three visits, blood samples were obtained for serum chemical analyses and complete blood cell counts with determination of differential fractions. Antibody values were measured at days 0 and 30, and at 1 year. Complete antibody panels and blood cell counts were not done on all children due to inadequate blood samples.

Laboratory Techniques

The following routine hematologic and metabolic values were determined by standard methods in the clinical laboratories at each study site: serum chloride, sodium, potassium, bicarbonate, glucose, alkaline phosphatase, urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, and total bilirubin; and complete blood cell count with total and differential leukocyte counts.

Specific immunologic responses were assayed at Lederle Biologicals. A modified enzyme-linked immunosorbent assay (ELISA) was used to determine lymphocytosis-promoting factor (LPF) and filamentous hemagglutinin (FHA) antibody concentrations, and microagglutination was used for determining

pertussis agglutinating antibodies. 11 Antitoxin values for tetanus were determined by neutralization in mice, 12 and diphtheria antitoxin values were determined using the rabbit skin test. 13

Vaccines

The DTP vaccine was a single lot of licensed Lederle vaccine (Tri-Immunol). which when studied met all government requirements for this vaccine. Endotoxin content was measured by the limulus amebocyte lysate assay and was 46 875 endotoxin units/0.5 mL of vaccine. Five endotoxin units equal 1 ng of Escherichia coli endotoxin in a normal assay; the effect of whole cells, adjuvant, and other factors make it impossible to establish with accuracy the real value of pertussis endotoxin in the vaccine. The APDT was formulated by Lederle Biologicals such that each dose contained 7.5 limit floculation units of diphtheria toxoid, 5 limit floculation units of tetanus toxoid, and 300 hemagglutinating units of Takeda acellular pertussis component. The diphtheria and tetanus toxoids were produced by Lederle Biologicals. The acellular pertussis component was manufactured by Takeda Chemical Industries and met all Japanese requirements for this vaccine. Components of the vaccine include LPF, FHA, and agglutinogens. This vaccine had an endotoxin content of 25 endotoxin units/0.5 mL.

Statistics

All antibody data were log-transformed before statistical analysis. Differences between APDT and DTP vaccine recipients for clinical reactions and fold change in antibodies were determined by Fisher's Exact Test. Antibody comparisons between vaccine groups were made by Wilcoxon's rank sum test. Wilcoxon's signed-rank test compared antibody values over time within vaccine groups. Differences for serum chemical analyses, white blood cell counts, and neutrophil and lymphocyte counts between days within each group were analyzed using the Student paired t test.

RESULTS Clinical Reactions

Local and systemic reactions that occurred within 48 hours of immunization in APDT and DTP vaccine recipients are compared in Table 1. In all instances except fever, a greater percentage of DTP vaccine recipients than APDT vaccinees had reactions, but the differences between the two vaccine categories were slight. Only pain and warmth at the injection site were significantly

Table 1.—Local and Systemic Reactions Within the First 48 Hours After

		保护的是不要的现在分词的	
Reactions	APDT (n = 41) No. (%)	DTP (n = 41) No. (%)	P
Local	AND VERY SERVICE		
Pain† Any	28 (68)	37 (90)	.03
Severe	0 (0)	3 (7)	.24
Erythema Any	15 (37)	22 (54)	.18
>20 mm	7 (17)	9 (22)	.78
Induration Any	11 (27)	16 (39)	.35
>20 mm	5 (12)	6 (15)	.99
Swelling Any	10 (24)	19 (46)	.06
>20 mm	5 (12)	11 (27)	.16
Site temperature Warm or hot	16 (39)	29 (71)	.007
Hot	2 (5)	3 (7)	.94
Systemic		A Product of the latest	
Oral temperature >38.0°C	5 (12)	5 (12)	1.0
>39.0°C	2 (5)	0	.49
Drowsiness Any	5 (12)	11 (27)	.16
Severe‡	0	0	1.0
Irritability Any	9 (22)	14 (34)	.33
Severe‡	0	1 (2)	.99
Anorexia	5 (12)	10 (24)	.25
Vomiting	0	3 (7)	.24

*APDT indicates acellular pertussis-component combined diphtheria and tetanus toxoids, and pertussis vaccine adsorbed; DTP, whole-cell combined diphtheria and tetanus toxoids, and pertussis vaccine adsorbed.

†Mild pain was defined as pain to the touch; moderate, spontaneous complaints of pain; and severe, pain limiting use of extremity.

\$Severe was defined as incapacitating, with inability to do usual activity.

Table 2.—Serum ELISA Antibody Responses to LPF in APDT and DTP Vaccine
Recipients*

Response APDT (n = 38) DTP (n = 40) P

Geometric mean Ells

APDT (n = 38)	DTP (n = 40)	P
6.8 (4.2-11.1)	5.6 (3.7-8.7)	.58
90.0 (63.2-119.6)	78.9 (56.1-111.0)	.73
12.8 (8.8-18.4)	14.0 (9.8-20.1)	.79
90%	88%	.99
84%	88%	.75
	6.8 (4.2-11.1) 90.0 (63.2-119.6) 12.8 (8.8-18.4) 90%	6.8 (4.2-11.1) 5.6 (3.7-8.7) 90.0 (63.2-119.6) 78.9 (56.1-111.0) 12.8 (8.8-18.4) 14.0 (9.8-20.1) 90% 88%

*APDT and DTP are defined in the first footnote to Table 1; ELISA indicates enzyme-linked immunosorbent assay; EUs, ELISA units; and LPF, lymphocytosis-promoting factor.

†Mean values in both APDT and DTP vaccine recipients were significantly higher on day 30 compared with day 0 (P<.0001).

more common in DTP vaccinees than in APDT recipients. Surprisingly, only 12% of all vaccinees (10) had fever. No severe local or systemic reactions occurred.

Serologic Responses

Serum antibody values to LPF, FHA, and agglutinogens before and after immunization with APDT and DTP

 Table 3.—Serum ELISA Antibody Responses to FHA in APDT and DTP Vaccine Recipients*

 Response
 APDT (n=38)
 DTP (n=40)
 P

 Geometric mean EUs (95% confidence interval) Day 0
 8.0 (5.4-11.9)
 6.3 (4.1-9.6)
 .4

 Day 30†
 222.2 (167.4-294.8)
 63.7 (46.0-88.0)
 <.0001</td>

10.1 (7.4-14.0)

88%

85%

<.0001

.06

*APDT and DTP are defined in the first footnote to Table 1; ELISA indicates enzyme-linked immunosorbent assay; EUs, ELISA units; and FHA, filamentous hemagglutinin.

27.8 (21.1-36.6)

100%

97%

Ratio of day 30/day 0

≥30 EUs at day 30

≥ Fourfold rise

†Mean values in both APDT and DTP vaccine recipients were significantly higher on day 30 compared with day 0 (P<.0001).

Table 4.—Serum Pertus	sis Agglutinin Response Recipients*	s in APDT and DTP Vacc	cine
Response	APDT (n = 32)	DTP (n = 36)	P
Reciprocal GMT (95% confidence interval)			
Day 0	42 (26-69)	29 (17-50)	.29
Day 30†	123 (78-193)	171 (112-261)	.19
Ratio of day 30/day 0	2.92 (1.99-4.28)	5.93 (3.99-8.80)	.01
≥1:32 at day 30	88%	94%	.41
≥ Fourfold rise	47%	72%	.05

*APDT and DTP are defined in the first footnote to Table 1; GMT indicates geometric mean titer.

†Reciprocal GMTs in both APDT and DTP vaccine recipients were significantly higher at day 30 compared with day 0 (P = .0001).

Response	APDT (n = 29)	DTP (n = 33)	P
Geometric mean EUs (95% confidence interval) Anti-LPF	17.7 (11.5-27.2)	22.9 (14.7-35.8)	40
Anti-FHA	49.1 (30.6-78.8)	10.8 (6.5-18.0)	.46
Anti-LPF ≥30 EUs	31%	49%	.20
Anti-FHA ≥30 EUs	69%	18%	<.001

*APDT and DTP are defined in the first footnote to Table 1; LPF indicates lymphocytosis-promoting factor; FHA, filamentous hemagglutinin; EUs, enzyme-linked immunosorbent assay units; and GMT, geometric mean titer.

vaccines are given in Tables 2 through 5. The mean ELISA antibody responses to LPF at day 30 after immunization were 90.0 ELISA units (EUs) in APDT vaccine recipients and 78.9 EUs in DTP vaccinees (Table 2). Ninety percent of APDT recipients (34) and 88% of DTP vaccinees (35) had antibody values greater than 30 EUs to LPF at 30 days

after immunization; 84% of APDT vaccine recipients (32) and 88% of DTP vaccine recipients (35) had at least fourfold anti-LPF rises in EUs.

Recipients of the APDT vaccine had a significantly better response to FHA than did DTP vaccinees (Table 3). At day 30 after immunization, the mean value antibody to FHA in APDT recipi-

ents was 222.2 EUs, whereas it was only 63.7 EUs in DTP vaccine recipients. All APDT vaccine recipients had antibody values greater than 30 EUs to FHA at day 30 after immunization, whereas 88% of DTP vaccinees (35) exceeded this value. Ninety-seven percent of APDT vaccinees (37) had at least a fourfold rise in FHA antibody, and 85% of DTP vaccine recipients (34) had a similar antibody response.

The agglutinin reciprocal geometric mean titer (GMT) at day 30 after immunization was 123 in APDT vaccine recipients and 171 in DTP vaccinees (Table 4). Eighty-eight percent of APDT vaccine recipients (28) and 94% of DTP vaccinees (34) had agglutinin titers of at least 1:32 on day 30 after immunization. Recipients of DTP vaccine had a greater day 30/day 0 ratio and a greater percentage of fourfold agglutinin titer rises than APDT vaccinees. In both APDT and DTP vaccine recipients, the day 30 agglutinin GMTs were significantly greater (P=.0001) than the day 0 GMTs.

Antibody responses at 1 year after immunization are shown in Table 5. Agglutinin titers and anti-LPF values were similar in APDT and DTP vaccine recipients at 1 year. The APDT vaccinees had a significantly higher anti-FHA value than did DTP vaccine recipients 1 year after immunization, and more APDT vaccinees had anti-FHA values greater than 30 EUs at that time.

Vaccinees had good booster responses to both tetanus and diphtheria toxoids with no significant differences observed between APDT and DTP vaccine recipients (data not shown).

Hematologic and Metabolic Tests

No specific clinically significant changes in the metabolic findings were noted on days 1 or 30 in the vaccinees. The mean serum glucose value on day 1 was 5.1 mmol/L in APDT vaccine recipients and 5.0 mmol/L in DTP vaccine recipients.

In Table 6, total white blood cell counts and absolute neutrophil and lymphocyte counts within a vaccine group over time and between vaccine groups are compared. On day 1, both APDT and DTP vaccine recipients had a significant increase in mean total leukocytes and neutrophils and a significant de-

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Table 6.—Comparison of Total Leukocyte Counts and Absolute Neutrophil and Lymphocyte Counts Within a Vaccine Group Over Time (Days 0, 1, and 30) and Between Vaccine Groups (APDT [n = 33] vs DTP [n = 37])*

	Day†			P Over Time		
Category	0	1	30	Day 0 vs 1	Day 0 vs 30	Day 1 vs 30
Total leukocytes, ×10°/L	•					
APDT	7.1 (6.4-7.8)	8.5 (7.7-9.2)	8.5 (7.6-9.4)	.0001	.0006	.95
DTP	7.2 (6.4-8.0)	9.2 (8.2-10.1)	7.4 (6.8-8.1)	.0001	.52	.0006
P‡	.89	.22	.06			
Total neutrophils, ×10°/L						
APDT	2.9 (2.4-3.3)	4.8 (4.2-5.3)	3.7 (2.9-4.4)	.0001	.03	.01
DTP	3.0 (2.5-3.6)	5.4 (4.6-6.3)	3.1 (2.5-3.7)	.0001	.83	.0001
P‡	.59	.16	.24			
Total lymphocytes, ×10°/L						
APDT	3.6 (3.2-4.1)	2.9 (2.6-3.3)	3.9 (3.6-4.3)	.0001	.18	.0002
DTP	3.5 (3.1-3.9)	3.0 (2.7-3.2)	3.7 (3.2-4.1)	.005	.55	.001
P‡	.76	.82	.36			

^{*}APDT and DTP are defined in the first footnote to Table 1.

crease in mean total lymphocytes. The APDT vaccine recipients had higher mean total leukocyte and neutrophil counts on day 30 than on day 0, whereas DTP vaccine recipients did not.

COMMENT

This study was the first of several trials with the Lederle-Takeda APDT vaccine in the United States. In contrast to the findings in previous studies with a similar APDT vaccine, 5-10 the rate and severity of most common reactions were similar in APDT and DTP vaccine recipients. This finding is not alarming because the reaction rate was low and the severity of the reactions was mild in both groups. In a previous large study, the following reaction rates were noted after the fifth DTP immunization with licensed US vaccines: erythema, 45%; swelling, 46%; pain, 74%; fever, 46%; drowsiness, 21%; fretfulness (irritability), 33%; anorexia, 17%; and vomiting, 4%. Reaction rates vary by vaccine lot, and for reasons that are unexplained, the control DTP vaccine used in our trial was less reactogenic than expected.14

In general, the immune responses to the major antigens (LPF, FHA, and agglutinogens) in the APDT vaccine were good. At day 30 after immunization, the agglutinin reciprocal GMT was 123 in APDT vaccine recipients, which

was a 2.92-fold increase in titer over the preimmunization value. Although DTP vaccinees increased agglutinin titers by twice as much as APDT vaccine recipients at day 30, the agglutinin reciprocal GMT at 1 year after immunization was similar in APDT vaccine recipients. The mean anti-LPF value at day 30 after immunization was 90.0 EUs in APDT vaccine recipients, which was a 12.8fold increase over the preimmunization value. The most remarkable immune response in APDT vaccine recipients was to FHA. The mean antibody value on day 0 was 8.0 EUs; it rose to 222.2 EUs on day 30. The FHA antibody response in APDT vaccinees was almost three times greater than that in DTP vaccine recipients; the mean anti-FHA value was 63.7 EUs at day 30 after immunization. At 1 year after immunization, APDT vaccine recipients continued to have higher anti-FHA values than DTP vaccinees.

Currently no serum antibody concentration to any of the pertussis antigens has been accepted as protective. Sato and Sato¹⁵ suggested that antibody values of 20 to 30 EUs/mL against LPF and FHA correlated with protection against pertussis. However, the recent Swedish trial¹⁶ to test the efficacy of two acellular pertussis vaccines failed to find a protective value for antibodies to either LPF or FHA. It was noted more than 30

years ago that the presence of serum agglutinins following immunization related to vaccine efficacy. 17-20 One study found that all 52 children with agglutinin titers of at least 1:320 were protected on household exposure, whereas 4 (24%) of 17 with titers of 1:160 or 1:80 experienced pertussis; 7 children had titers of 1:40 or lower, and all but 1 had pertussis. Unfortunately, there is no way to compare titers resulting from currently performed agglutinin assays with those in the studies mentioned above. Current Food and Drug Administration policy is such that equivalency of serologic responses between DTP vaccine and an APDT vaccine is not sufficient for licensure of the new product.

The metabolic and hematologic findings in this study are of interest. In animal experiments, pertussis vaccine causes leukocytosis with a predominant lymphocytosis and hypoglycemia.1 These effects are mainly due to LPF, but endotoxin (lipopolysaccharide) could also contribute to the findings. In this trial, both vaccine groups had normal mean serum glucose values at days 1 and 30 after immunization. In contrast with the serum glucose values, mild leukocytosis, neutrophilia, and lymphopenia were observed following immunization in recipients of both APDT and DTP vaccines. This effect

[†]Values are means (95% confidence interval).

[‡]P compares APDT vs DTP.

would appear not to be due to LPF since lymphocytosis did not occur. It may be due to endotoxin, but since the amount of endotoxin apparently is so greatly reduced in the APDT vaccine, the al-

most similar response in APDT and DTP recipients is surprising.

In conclusion, the APDT vaccine studied in this trial was less reactogenic than DTP vaccine while resulting in

good antibody responses in 4- to 6-yearold children. Further studies are under way in larger groups of children as well as younger age groups.

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Adolescent Acquired Immunodeficiency Syndrome

A Paradigm for Training in Early Intervention and Care

Karen Hein, MD

The human immunodeficiency virus (HIV) epidemic may portend disaster or may become an opportunity for learning some of the basic lessons of medicine for those entering the ranks of health care workers in the 1990s. At present, a small cadre of health care professionals have dedicated themselves exclusively to the care of HIV-infected people. Although their number has increased in the past 8 years, they still represent a tiny fraction of total health care professionals. As they age or burn out, who will be there to take their places?¹

Major academic medical centers on the East and West coasts have not filled residency training slots with the candidates of their choice for the past several years. One of the reasons given by candidates and feared by training directors is the acquired immunodeficiency syndrome (AIDS) epidemic. The muchpublicized strain on existing resources, the emotional drain caused by caring for terminally ill infants and young adults, and, perhaps, the undue fear of contracting HIV in the workplace may be contributing factors.

Educating future health care workers requires some insight into the factors that motivate people to work in specific areas of medicine. Why do some health care workers choose to become involved in the epidemic? Some find themselves in the midst of an epidemic and are doing

what needs to be done. Others have been attracted to becoming involved in the epidemic because of ideologic or political views. Some health professionals' lives have been touched personally through knowledge of someone who is infected. Others are drawn to the epidemic because it represents a new frontier, an area that challenges all the givens and stretches the limits of what is known into the realm of what needs to be known. Who will be the next generation of health care professionals to fill the ranks created by these few? Can the training programs keep up with the epidemic as HIV spreads throughout the United States and the world? Right now, approximately 58% of people with AIDS are treated in only 28 hospitals. Currently, 80% of reported cases come from a handful of urban areas, but by 1991 it is estimated that only 20% of the cases will be in these locales and 80% will be in the rest of the United States (The New York Times. June 20, 1989:B1-B2). Who will be there to take care of the people?

Many organizations and leading health authorities have begun to recommend routine offering of HIV counseling and testing despite the fact that adequate services including adequately trained health personnel are lagging behind (The Nation's Health. July 1989: 1,7). In Fig 1, the number of people infected with HIV in 1989 is depicted along with the number projected to be infected by 1992. The shaded area represents the segment of the total HIVinfected population where most of the resources are currently focused. Right now, services (and training) are focused on people who are symptomatic with HIV-related illnesses or who have AIDS, particularly those who are in the terminal phase of their illness. Acquired immunodeficiency syndrome is rising rapidly in the ranks of the leading causes of death among children.² Acquired immunodeficiency syndrome is already the ninth leading cause of death among children 1 to 4 years of age, and is the seventh leading cause in young people aged 15 to 24 years.

In Fig 2, the shaded area represents the rest of the HIV-infected population. This group includes those who are recently infected, those who are asymptomatic, and those whose symptoms have only begun to become apparent. The vast majority of these people do not know that they are infected.3 With the increased emphasis on HIV testing, the ranks of those who know their seropositive status will grow quickly over the next few years. Already there is evidence that people with AIDS are traveling from the suburbs and rural areas to major urban areas for health care because of the lack of comprehensive services or knowledgeable people to care for them close to home (The New York Doctor. January 30, 1989). The valuable experiences of people working in the HIV epicenters could form the foundation for others to learn about both the art and science of medicine in the 21st century.

The history of medicine is replete with other examples of epidemics that have resulted in great leaps in public health. The lessons learned from the epidemics of syphilis, tuberculosis, and polio were all eventually incorporated into the training programs for health care professionals during the 20th century. Educational elements go far beyond the pathophysiology of the disease or the available treatments. Over 100 000 cases of AIDS have been reported in the United States. Roughly one half of people with AIDS have died.

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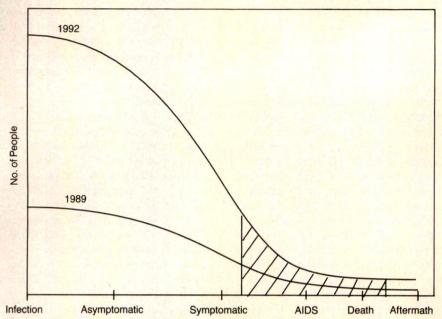


Fig 1.—The number of people estimated to be infected with the human immunodefiency virus in 1989 and 1992. The shaded area represents the current concentration of services and resources.

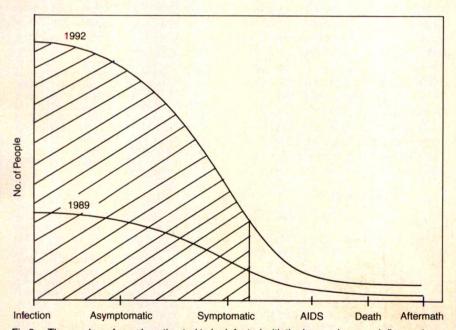


Fig 2.—The number of people estimated to be infected with the human immunodefiency virus. The shaded area represents the large proportion of asymptomatic people requiring early intervention and care and a new focus in resources and services.

One to 1.5 million people in the United States are probably HIV infected. What if all the people who are HIV seropositive suddenly knew it. Where would they all go? Who would be there for them when they got there?

The HIV epidemic raises serious and imminent issues in the training of health

care professionals who care for children and adolescents (*The American Academy of Pediatrics News.* November 1987:2; August 1988:2). The HIV epidemic will be with us for the foreseeable future (*The New York Times.* March 3, 1989:B3). The recently documented problem of viral resistance to antiviral

The Elements of Early Intervention and Care of Human Immunodeficiency Virus–Infected People

Counseling	Follow-up Care	Treatments*
Person, partner, family	Medical, psychosocial, nutritional, legal	AZT, PCP, TB, STD

*Treatment regimens include zidovudine (AZT), pentamidine (PCP), and medication for various stages of tuberculosis (TB) and sexually transmitted disease (STD).

drugs has already complicated the use of approved therapies. Even with improved treatments, based on the number of infected people, all health care professionals will have to become versed in HIV-related issues (*The Nation's Health*. August 1989:1-3). Analyses of federal spending for illness caused by HIV have not included separate consideration for training the next generation of professionals.

Where, then, can we look for ways to organize care, to organize training, and to find ways to incorporate this new training into existing health systems? Adolescents with HIV are an appropriate group to learn about the principles of early intervention and care. 6 Although only 1% of total reported cases of AIDS are in people aged 13 to 21 years, many people with AIDS in their 20s (21% of cases) were infected as adolescents. The profile of transmission-associated categories in adolescents differs from that recorded in children or adults. Approximately three quarters of all cases in childhood are attributed to an infected parent, usually because the mother or her partner was an intravenous drug user. A higher percent of cases in adolescents (8%) are due to heterosexual spread than in adults (4%).8 In New York, NY, adolescents, the percent attributed to heterosexual contact is 15%.9 Among New York City adolescents, the male to female ratio is 3:1. In female adolescents, 48% of cases outside New York City and 52% of cases among New York City adolescents are due to heterosexual spread. Given what we know about other sexually transmitted diseases, such as gonorrhea and syphilis, once HIV has entered the adolescent population, it is likely to spread

rapidly but silently, since the average period of latency from infection to disease is now estimated to be 9 years. Female adolescents have the highest rates of reported sexually transmitted diseases of any age group when rates are corrected for the percent of sexually active people in each age category. 10

Seroprevalence studies from various subpopulations of adolescents document the fact that HIV has entered the adolescent community. Rates of HIV seropositivity among military recruits aged 16 to 20 years," members of the Job Corps, 12 infants born to teenage mothers, 13 and entrants to a youth shelter program (J. Kennedy, testimony before the Presidential Commission on the HIV epidemic, May 1988) amply demonstrate that HIV has entered various segments of the American adolescent population. The portrait of the epidemic in adolescents points to a more central role for heterosexual spread than has been demonstrated in adults to date. The skills required to take an age-appropriate social and sexual history, to perform appropriate physical examinations (including pelvic and genital examinations when indicated), and to counsel regarding the pros and cons of HIV antibody testing, use of contraceptives, the use of prophylactic treatments for opportunistic infection, and the appropriate laboratory assessment of HIV-seropositive individuals are only a few examples of the type of skills

that need to be inculcated for proper training of health care professionals.

As shown in the Table, the elements of early intervention and care include evaluation, counseling, follow-up care, and treatments. Counseling should be centered on the individual who is at risk. Ideally, partner(s) and family members should be included. Laws and guidelines governing anonymity, confidentiality, and disclosure of HIV-related information are examples of information that providers must have to do adequate counseling. Skill at individual, couple, and group interviewing are essential to properly conduct these counseling sessions. Evaluation and follow-up care require expertise in medical, psychosocial, nutritional, and legal issues.14 Examples of treatment regimens that are frequently indicated for HIV-seropositive people include zidovudine, pentamidine, and medication for various stages of tuberculosis and sexually transmitted diseases. Some of the components of these services are standard for any child or adolescent, yet others are HIV-specific due to the effect of HIV on growth, cofactors that may exacerbate HIV progression, or the specific effect on social and psychological function due to stigmatization or discrimination.

At the moment, we look to those most experienced in caring for HIV-infected youth for guidance in developing policies, protocols, and coping strategies for the health care professionals as well as the at-risk or HIV-seropositive children and youth. However, in the next 5 years this type of expertise will have to become more widespread. The epidemic in the United States is part of a worldwide pandemic. After completion of training, these skills will be in demand. Communities expect (rightfully so) that health care professionals should be knowledgeable about HIV. Patients and families have fears and questions. Schools need input on policies about AIDS education and HIV-infected employees and students (The American Academy of Pediatrics News. June 1988:9). Businesses need input about fair employment practices. It has been amply demonstrated that individuals and whole communities can respond with compassion to HIV-infected people. However, many fears, misconceptions, and gaps in knowledge must first be addressed. Medical education for health care professionals can and must now include specific information about the medical, psychological, and social aspects of HIV. It is time to spread the word, not the virus!

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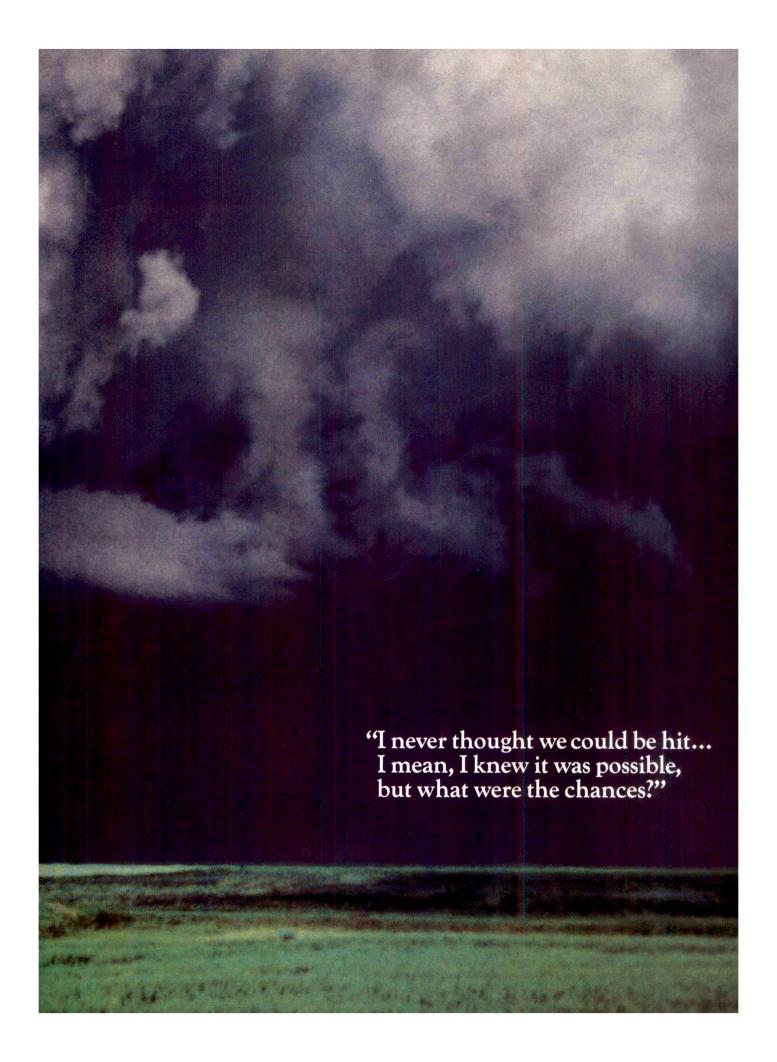
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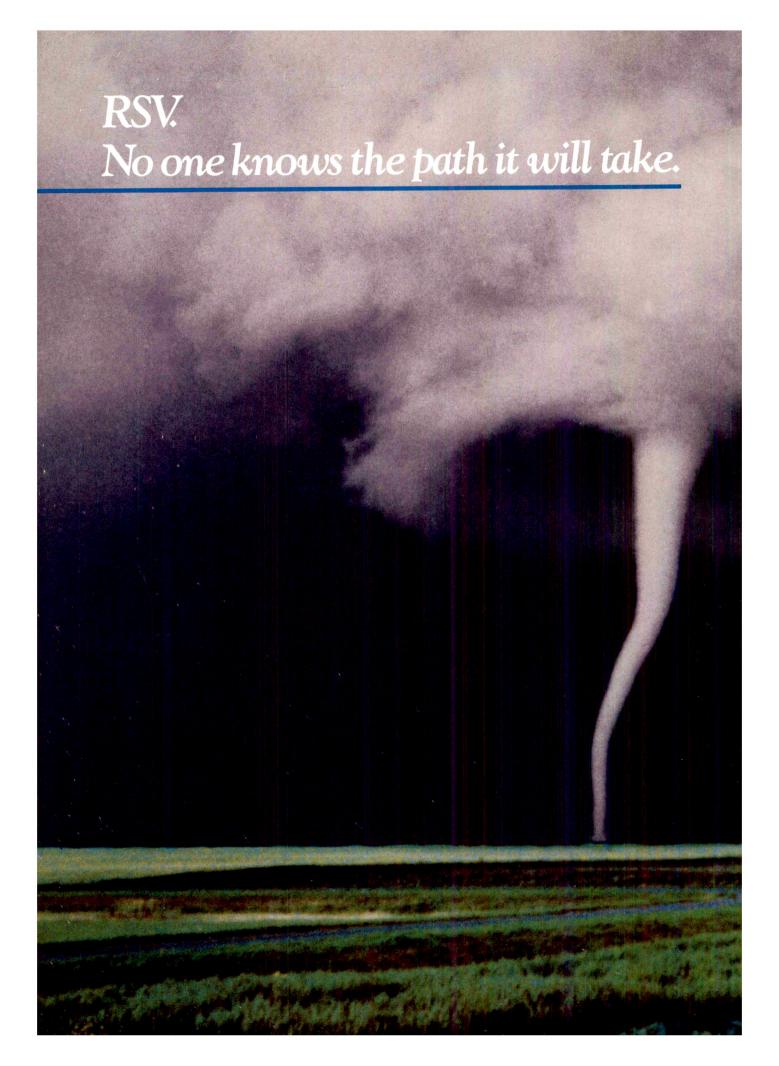
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The consequences may have a lasting effect. The short-term consequences of respiratory syncytial virus (RSV) infection can include nosocomial spread, mechanical ventilation, extended hospitalization—even death—and can threaten all hospitalized children under 4 years old. Respiratory viral infections may have a long-term effect on the respiratory tree in some patients, such as development of bronchopulmonary disease.¹

Help reduce the toll taken by

RSV. In clinical experience with over 50,000 patients, treatment of appropriate patients with Virazole® (ribavirin) Aerosol improved disease symptoms safely, speeding recovery²⁻⁶ while significantly reducing viral shedding.^{2,4} Virazole may reduce the need for supplemental oxygen and mechanical ventilation.⁷ And Virazole has been shown to prevent development of RSV-specific IgE responses,⁸ which may correlate with the release of histamine and clinical expression of obstructive reactive airway disease.¹

Serious enough to hospitalize, serious enough to consider

Virazole® (ribavirin)

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PRESCRIBING INFORMATION

WARNING: RIBAVIRIN AEROSOL SHOULD NOT BE USED FOR INFANTS REQUIRING ASSISTED VENTILATION BECAUSE PRECIPI-TATION OF THE DRUG IN THE RESPIRATORY
EQUIPMENT MAY INTERFERE WITH SAFE AND EFFECTIVE VENTILATION OF THE PATIENT. Conditions for safe use with a ventilator are still in development.

Deterioration of respiratory function has been associated with ribavirin use in infants, and in adults with chronic obstructive lung disease or asthma. Respiratory function should be carefully monitored during treatment. If initiation of ribavirin aerosol treatment appears to produce sudden deterioration of respiratory function, treatment should be stopped and re-instituted only with extreme caution and

continuous monitoring.

Although ribavirin is not indicated in adults, the physician should be aware that it is teratogenic in animals (see CONTRAINDICATIONS).

DESCRIPTION:

Virazole® (ribavirin) Aerosol, an antiviral drug, is a sterile, lyophilized powder to be reconstituted for aerosol administration. Each 100 ml glass vial contains 6 grams of ribavirin, and when reconstituted to the recommended volume of 300 ml with sterile water for injection or sterile water for inhalation (no preservatives added), will contain 20 mg/ml ribavirin, pH approximately 5.5. Aerosolization

is to be carried out in a SPAG-2 nebulizer only.

Ribavirin is 1-beta-D-ribofuranosyl-1,2,4-triazole-3-carboxamide, with the following structural formula:



Ribavirin, a synthetic nucleoside, is a stable, white, crystalline compound with a maximum solubility in water of 142 mg/ml at 25°C and with only a slight solubility in ethanol. The empirical formula is C₈H₁₂N₄O₅ and the molecular weight is 244.2 Daltons.

CLINICAL PHARMACOLOGY:

Antiviral effects:

Ribavirin has antiviral inhibitory activity in vitro against respiratory syncytial virus, influenza virus, and herpes simplex virus. Ribavirin is also active against respiratory syncytial virus (RSV) in experimentally infected cotton rats.

In cell cultures, the inhibitory activity of ribavirin for RSV is selective. The mechanism of action is unknown. Reversal of the in vitro antiviral activity by guanosine or xanthosine suggests ribavirin may act as an analogue of these cellular metabolites.

Immunologic effects:

Neutralizing antibody responses to RSV were decreased in ribavirin treated compared to placebo treated infants.³ The clinical significance of this obseration is unknown. In rats, ribavirin resulted in lymphoid atrophy of thymus, spleen, and lymph nodes. Humoral immunity was reduced in guinea pigs and ferrets. Cellular immunity was also mildly depressed in animal studies

Microbiology:

Several clinical isolates of RSV were evaluated for ribavirin susceptibility by plaque reduction in tissue culture. Plaques were reduced 85.98% by 16 μ g/ml; however, plaque reduction varies with the test system. The clinical significance of these data is unknown

Pharmacokinetics:

Assay for ribavirin in human materials is by a radioimmunoassay which detects ribavirin and at least one

Ribavirin administrered by aerosol is absorbed systemically. Four pediatric patients inhaling ribavirin aerosol administered by face mask for 2.5 hours each day for 3 days had plasma concentrations ranging from 0.44 to 1.55 μ M, with a mean concentration of 0.76 μ M. The plasma half-life was reported to be 9.5 hours. Three pediatric patients inhaling ribavirin aerosol administered by face mask or mist tent for 20 hours each day for 5 days had plasma concentrations ranging from 1.5 to 14.3 µM. with a mean concentration of 6.8 μ M

It is likely that the concentration of ribavirin in respiratory tract secretions is much higher than plasma concentrations in view of the route of administration

The bioavailability of ribavirin aerosol is unknown and may depend on the mode of aerosol delivery. After aerosol treatment, neak plasma concentrations are less than the concentration that reduced RSV plaque formation in tissue culture by 85 to 98%. After aerosol treatment, respiratory tract secretions are likely to contain ribavirin in concen-trations many fold higher than those required to reduce plaque formation. However, RSV is an intracellular virus and serum concentrations may better reflect intracellular concentrations in the respiratory tract than respiratory secretion concentrations.

In man, rats, and rhesus monkeys, accumulation of ribavirin and/or metabolites in the red blood cells has been noted, plateauing in red cells in man in about 4 days and gradually declining with an apparent half-life of 40 days. The extent of accumulation of ribavirin following inhalation therapy is not well defined.

INDICATIONS AND USAGE:

Ribavirin aerosol is indicated in the treatment of carefully selected hospitalized infants and young children with severe lower respiratory tract infections due to respiratory syncytial virus (RSV). In two placebo-controlled trials in infants hospitalized with RSV lower respiratory tract infection, ribavirin aerosol treatment had a therapeutic effect, as judged by the reduction by treatment day 3 of severity of clinical manifestations of disease. 3.4 Virus titers in respiratory secretions were also significantly reduced with ribavirin in one of these studies.

Only severe RSV lower respiratory tract infection is to be treated with ribavirin aerosol. The vast majority of infants and children with RSV infection have no lower respiratory tract disease or have disease that is mild, self-limited, and does not require hospitalization or antiviral treatment. Many children with mild lower respiratory tract involvement wil require shorter hospitalization than would be required for a full course of ribayirin aerosol (3 to 7 days) and should not be treated with the drug. Thus the decision to treat with ribavirin aerosol should be based on the severity of the RSV

The presence of an underlying condition such as pre maturity or cardiopulmonary disease may increase the severity of the infection and its risk to the patient. High risk infants and young children with these underlying conditions may benefit from ribavirin treatment, although efficacy has been evaluated in only a small number of such

Ribavirin aerosol treatment must be accompanied by and does not replace standard supportive respiratory and fluid management for infants and children with severe respiratory tract infection.

Diagnosis:

RSV infection should be documented by a rapid diagnostic method such as demonstration of viral antigen in respiratory tract secretions by immunofluorescence^{3,4} or ELISA5 before or during the first 24 hours of treatment Ribavirin aerosol is indicated only for lower respiratory tract infection due to RSV. Treatment may be initiated while awaiting rapid diagnostic test results. However, treatment should not be continued without documentation of RSV infection

CONTRAINDICATIONS:

Ribavirin is contraindicated in women or girls who are or may become pregnant during exposure to the drug. Ribavirin may cause fetal harm and respiratory syncytial virus infection is self-limited in this population. Ribavirin is not completely cleared from human blood even four weeks after administration. Although there are no pertinent human data, ribayirin has been found to be teratogenic and/or embryolethal in nearly all species in which it has been tested. Teratogenicity was evident after a single oral dose of 2.5 mg/kg in the hamster and after daily oral doses of 10 mg/kg in the rat. Malformations of skull, palate, eye, jaw, skeleton, and gastrointestinal tract were noted in animal studies. Survival of fetuses and offspring was reduced. The drug causes embryolethality in the rabbit at daily oral dose levels as low as 1 mg/kg.

WARNINGS:

Ribavirin administered by aerosol produced cardiac lesions in mice and rats after 30 and 36 mg/kg, respectively, for 4 weeks, and after oral administration in monkeys at 120 and rats at 154 to 200 mg/kg for 1 to 6 months. Ribavirin aerosol administered to developing ferrets at 60 mg/kg for 10 or 30 days resulted in inflammatory and possible emphysematous changes in the lungs. Proliferative changes were seen at 131 mg/kg for 30 days. The significance of these findings to human administration is

Ribavirin lyophilized in 6 gram vials is intended for use as an aerosol only

PRECAUTIONS:

General:

Patients with lower respiratory tract infection due to respiratory syncytial virus require optimum monitoring and attention to respiratory and fluid status.

Drug Interactions:

Interactions of ribavirin with other drugs such as digoxin, bronchodilators, other antiviral agents, antibiotics, or antimetabolites has not been evaluated. Interference by ribavirin with laboratory tests has not been evaluated.

Carcinogenesis, mutagenesis, impairment of

Ribavirin induces cell transformation in an in vitro mam malian system (Balb/C3T3 cell line). However, in vivo carcin ogenicity studies are incomplete. Results thus far, though inconclusive, suggest that chronic feeding of ribavirin to rats at dose levels in the range of 16-60 mg/kg body weight can induce benign mammary, pancreatic, pituitary and adrenal tumors.

Ribavirin is mutagenic to mammalian (L5178Y) cells in culture. Results of microbial mutagenicity assays and a dominant lethal assay (mouse) were negative.

Ribavirin causes testicular lesions (tubular atrophy) in adult rats at oral dose levels as low as 16 mg/kg/day (lower doses not tested), but fertility of ribavirin-treated animals (male or female) has not been adequately investigated. Pregnancy:

Teratogenic Effects: Pregnancy Category X. See "Contraindications" section.

Nursing Mothers: Use of ribavirin aerosol in nursing mothers is not indicated because RSV infection is selflimited in this population. Ribavirin is toxic to lactating animals and their offspring. It is not known whether the drug is excreted in human milk

ADVERSE REACTIONS:

Approximately 200 patients have been treated with ribavirin aerosol in controlled or uncontrolled clinical

Pulmonary function significantly deteriorated during ribavirin aerosol treatment in six of six adults with chronic obstructive lung disease and in four of six asthmatic adults. Dyspnea and chest soreness were also reported in the latter group. Minor abnormalities in pulmonary function were also seen in healthy adult volunteers.

Several serious adverse events occurred in severely ill infants with life-threatening underlying diseases, many of whom required assisted ventilation. The role of ribavirin aerosol in these events is indeterminate. The following events were associated with ribavirin use

Pulmonary: Worsening of respiratory status, bacterial pneumonia, pneumothorax, apnea, and ventilator

Cardiovascular: Cardiac arrest, hypotension, and digitalis

There were 7 deaths during or shortly after treatment with ribavirin aerosol. No death was attributed to ribavirin aerosol by the investigators.

Some subjects requiring assisted ventilation have experienced serious difficulties, which may jeopardize adequate ventilation and gas exchange. Precipitation of drug within the ventilatory apparatus, including the endotracheal tube, has resulted in increased positive end expiratory pressure and increased positive inspiratory pressure Accumulation of fluid in tubing ("rain out") has also been

Although anemia has not been reported with use of the aerosol, it occurs frequently with oral and intravenous ribavirin, and most infants treated with the aerosol have not been evaluated 1 to 2 weeks post-treatment when anemia is likely to occur. Reticulocytosis has been reported with aerosol use.

Rash and conjunctivitis have been associated with the use of ribavirin aerosol.

Overdosage:

No overdosage with ribavirin by aerosol administration has been reported in the human. The LD50 in mice is 2 gm orally. Hypoactivity and gastrointestinal symptoms occurred. In man, ribavirin is sequestered in red blood cells for weeks after dosing.

DOSAGE AND ADMINISTRATION

Before use, read thoroughly the Viratek Small Particle Aerosol Generator (SPAG) Model SPAG-2 Operator's Manual for small particle aerosol generator operating instructions.

Treatment was effective when instituted within the first 3 days of respiratory syncytial virus lower respiratory tract infection.3 Treatment early in the course of severe lower respiratory tract infection may be necessary to achieve

Treatment is carried out for 12-18 hours per day for at least 3 and no more than 7 days, and is part of a total treatment program. The aerosol is delivered to an infant oxygen hood from the SPAG-2 aerosol generator. Administration by face mask or oxygen tent may be necessary if a hood cannot be employed (see SPAG-2 manual). However, the volume of distribution and condensation area are larger in a tent and efficacy of this method of administering the drug has been evaluated in only a small number of patients. Ribayirin aerosol is not to be administered with any other aerosol generating device or together with other aerosolized medications. Ribavirin aerosol should not be used for patients requiring simultaneous assisted ventilation (see Boxed Warnings).

Virazole is supplied as 6 grams of lyophilized drug per 100 ml vial for aerosol administration only. By sterile technique, solubilize drug with sterile USP water for injection or inhalation in the 100 ml vial. Transfer to the clean, sterilized 500 ml widemouth Erlenmeyer flask (SPAG-2 Reservoir) and further dilute to a final volume of 300 ml with sterile USP water for injection or inhalation. The final concentration should be 20 mg/ml. Important: This water should not have had any antimicrobial agent or other substance added. The solution should be inspected visually for particulate matter and discoloration prior to administration. Solutions that have been placed in the SPAG-2 unit. should be discarded at least every 24 hours and when the liquid level is low before adding newly reconstituted

Using the recommended drug concentration of 20 mg/ml ribavirin as the starting solution in the drug reservoir of the SPAG unit, the average aerosol concentration for a 12 hour period would be 190 micrograms/liter (0.19 mg/l) of air.

HOW SUPPLIED:

Virazole® (ribavirin) Aerosol is supplied in 100 ml glass vials with 6 grams of sterile, lyophilized drug which is to be reconstituted with 300 ml sterile water for injection or sterile water for inhalation (no preservatives added) and administered only by a small particle aerosol generator (SPAG-2). Vials containing the lyophilized drug powder should be stored in a dry place at 15:25°C (59:78°F) Reconstituted solutions may be stored, under sterile conditions, at room temperature (20-30°C, 68-86°F) for 24 hours. Solutions which have been placed in the SPAG-2 unit should be discarded at least every 24 hours.

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Clinical Experience With Fetal Echocardiography

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· Current ultrasound technology allows for accurate evaluation of the fetal heart. To evaluate the importance and accuracy of the routine clinical use of fetal echocardiography at our center, a consecutive series of 338 fetal cardiac studies of 323 patients was reviewed. Average gestational age was 24 weeks (range, 17 to 39 weeks). Forty-seven (15%) patients with abnormal conditions were detected. The most common indication for fetal cardiac scan was a family history of congenital heart disease (28%). Other indications were maternal diabetes mellitus (25%), fetal dysrhythmia (14%), other major defect (10%), drug exposure (10%), and obstetrician suspicion of fetal congenital heart disease on routine scan (10%). The highest yield of significant abnormal findings was among those referred for dysrhythmia (31%) and obstetrician suspicion of congenital heart disease (29%). Five fetuses with sustained supraventricular tachycardia and hydrops were successfully treated. The combination of fetal bradycardia and structural heart disease was the most ominous finding. Fifteen (4.6%) patients had clear changes in management based on the fetal echocardiogram. Our experience suggests that the routine use of fetal echocardiography is accurate and an important part of the overall management of the pregnancy considered at risk for producing an infant with congenital heart disease.

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R ecent advances in two-dimensional and Doppler echocardiography permit accurate examination of the heart of the fetus. The capability for such evaluation is likely to increase in the future. The pediatrician—a primary care provider for the family with a child with congenital heart disease (CHD)—as well as the obstetrician and pediatric

cardiologist are involved with this "new" population of patients.

The technique, accuracy, safety, and clinical importance of fetal echocardiography have been reported. 1-10 An infant with a recognized major cardiac defect in utero can benefit from delivery at a center with appropriate pediatric cardiovascular services. In addition to identification of structural anomalies, accurate diagnosis of fetal cardiac dysrhythmias can allow for successful transplacental treatment. 11-18 Identification of a severe cardiac defect can permit making an informed decision regarding management of the pregnancy. Since cardiac defects often coexist with other major organ system defects, 4,14 identification of a normal or abnormal heart can impact on decisions regarding overall outcome of the pregnancy.

METHODS

A 4-year clinical experience with fetal echocardiography at Columbus Children's Hospital and Ohio State University was evaluated with regard to accuracy of diagnosis, reasons for referral, frequency of fetal heart defects within our referred population, and overall effects of the fetal echocardiogram on pregnancy management and outcome.

All studies were performed with a Hewlett-Packard phased array device (Sonos 500 77020AC, Hewlett Packard, Andover, Mass) with a spatial peak temporal average energy output less than 100 mW/cm². During the last 18 months of the reported series, Doppler evaluation became a routine part of the examination when a defect was suspected by image. Verbal informed consent was obtained for all procedures. Studies were considered to be a clinical diagnostic evaluation aimed at providing important information for the patient. All but one study was by the standard transabdominal approach. One examination was transvaginal.

Patients were referred for fetal echocardiography for one or more of the following risks: family history of CHD; insulin-dependent diabetes mellitus; fetal dysrhythmia; drug exposure; other major fetal defect; and obstetrician suspicion of CHD from ultrasound scan. All initial referrals were from the Department of Obstetrics at the Ohio State University. During the fourth year of the series this source accounted for 60% of all referrals, with the remainder coming from community practitioners in central and southeastern Ohio. The total population base of our referral area is 3.5 million, with approximately 40 000 annual deliveries.

A total of 338 studies were performed on 323 patients from August 1985 to August 1989. Studies were judged to be of adequate diagnostic quality if the following were defined: cardiac situs; cardiac rhythm; ventricular and atrial chambers; valves; and the aortic and pulmonary arterial connections to the heart. An attempt was made at each examination to visualize the aortic and ductal arches. M-mode recordings were done only if an abnormality was identified by two-dimensional imaging, or for evaluation of dysrhythmia. Measurements of ventricular size were made from two-dimensional recordings and compared with published normal values. Color and pulsed Doppler echocardiography were done only when a significant defect was suspected by imaging. All data were maintained in a computer database with the following data fields: patient name, date of procedure, fetal age, referring source, reason for referral, quality of study, diagnosis, and follow-up history.

RESULTS

Of the 323 patients, 13 had one repeated examination and 1 patient had 2 repeated examinations for a total of 338 fetal echocardiograms. Average gestational age was 24 weeks (range, 17 to 39 weeks). Eight patients had repeated examinations for follow-up of an abnormality, and 6 examinations were repeated because of a nondiagnostic initial study. Diagnostic quality fetal echocardiograms were obtained in 319 patients. Despite repeated examination of 4 patients, including a transvaginal approach in 1, imaging was inadequate. In each instance, imaging was virtually impossible because of a combination of maternal obesity and unfavorable fetal position. The best fetal position for cardiac imaging was with chest anterior and abdomen upward toward the scanning

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Indication*		(%) of ients		Patie	(%) of nts With I Conditions
Family history of CHD	91	(28)		3	(3)
Maternal diabetes	80	(25)		4	(5)
Dysrhythmia	. 45	(14)		25	(56)
Other major defect	34	(10)		. 6	(18)
Drug exposure	32	(10)		0	(0)
OB suspects CHD	31	(10)	1	9	(29)
Miscellaneous	10	(3)		0	(0)
Total	, 323	(100)		47	(15)

^{*}CHD denotes congenital heart disease; OB, obstetrician.

transducer. Other positions frequently resulted in shadowing effects of rib and spine. On several occasions, adequate studies were obtained only after having the mother walk, resulting in a subsequent favorable change in fetal position.

consistently highest-quality studies were observed at fetal age near 20 weeks. Because of this, referring practitioners were encouraged to schedule patients for fetal echocardiograms at about 20 weeks. The fetus at term was often more difficult to image because of the normally decreased amount of amniotic fluid, decreased movement that would not allow for position change, and increased ossification of bony structures that resulted in shadowing. The average time required for a study of normal fetuses was 30 minutes, with that of abnormal fetuses often requiring up to an hour.

Postnatal follow-up of 260 infants showed that five diagnostic errors occurred. As all infants have not been born and evaluated, there may be additional errors that are as yet undetected. All but one of the fetuses that have been delivered, with abnormalities detected by fetal scan, have had neonatal evaluation.

One error was made in diagnosing a fetus studied at 25 weeks for dysrhythmia. This was the 10th patient of the series. Second-degree atrioventricular block was correctly diagnosed. The heart was described as structurally normal. After delivery, the correct diagnosis of 1-transposition of the great arteries was made. This child developed a complete heart block (CHB) at 2 weeks of age. Another error occurred in a fetus studied at 35 weeks. A moderate-to-

large muscular ventricular septal defect (VSD) was found. During postnatal follow-up echocardiography, moderate valvular aortic stenosis was also detected. One infant was found to have a nonstenotic bicuspid aortic valve and coarctation of aorta in which the fetal study was reported as normal. Another infant was found to have mild valvular aortic stenosis and aortic coarctation in which the fetal study showed only the abnormal aortic valve. Neither patient has required surgical coarctation repair. The fifth error occurred in a fetus diagnosed only as having a markedly dilated umbilical vein, found after birth to have a secundum atrial septal defect (ASD). The correct diagnosis of large ASD was suspected in two other fetal examinations due to a virtually complete absence of any atrial septum with high-quality imaging. Because of the variable appearance of the atrial septum of the fetus, and because the foramen ovale is in the same location, diagnosis of secundum ASD may be difficult.

Forty-seven (15%) patients with abnormal results were detected among the 323 studied. Excluding unsustained atrial dysrhythmia, 35 significant abnormal conditions were found (11%). All but one of these fetuses have been delivered, and their abnormalities confirmed by clinical/echocardiographic/catheterization evaluation as appropriate, or by autopsy. Autopsy was denied in two elective abortions. One of these was a fetus with trisomy 18, with a large VSD and small left heart. The other was a fetus with atrial isomerism, atrioventricular septal defect (AVSD), CHB, and hydrops. Autopsy was also denied in one instance of in utero death of a fetus with hypoplastic left heart and supraventricular tachycardia (SVT).

The most common indication for fetal cardiac scan was a family history of CHD (Table 1). In each instance, a first-degree family member was affected. Three fetuses (3%) scanned for this reason were found to have significant cardiac defects. One patient with a fetus with VSD and valve aortic stenosis had two other children with VSD, and one patient with ASD and Holt-Oram syndrome had a fetus with the same problems. Another patient with a fetus with VSD had a child with VSD and aortic coarctation.

The second most common reason for scan was insulin-dependent maternal diabetes. Our major source of referrals is the Ohio State University Hospitals, where evaluation of maternal diabetes is a major interest. Four fetuses scanned for this indication had significant CHD. The following defects were found: Ebstein's malformation of the tricuspid valve; polysplenia syndrome with AVSD and left ventricular outflow obstruction; secundum ASD; and tetralogy of Fallot with pulmonary atresia. Thus, 4 (5%) of 80 fetuses scanned because of maternal diabetes had CHD.

Fetal dysrhythmia was the primary reason for referral in 45 (14%) of the 323 patients evaluated. Of these 45 patients, 24 (53%) were found to have dysrhythmia, 11 had insignificant unsustained atrial ectopy, and 13 (29%) had significant dysrhythmia. One patient studied for dysrhythmia was described as showing normal results. However, follow-up revealed mild valvular aortic stenosis and coarctation of the aorta. A total of 15 patients (5%) in the series of 323 were found to have significant dysrhythmia (Table 2). Five fetuses had sustained SVT with associated hydrops. All five were successfully treated with maternally administered digoxin and either quinidine sulfate or procainamide hydrochloride. Each one is well, at the 6-month to 2-year followup. Two have the Wolff-Parkinson-White syndrome. One fetus with SVT and hydrops also had hypoplastic left heart and was a spontaneous in utero death. Two fetuses had sinus/junctional bradycardia. One of these had a normal heart but died several days after the echocardiogram taken at 22 weeks,

Table 2.—Fetal Dysrhythmias			
Type of Dysrhythmia*	No. (%) of Patients		
Unsustained atrial			
Isolated PACs	10 (37.0)		
Bigeminy	2 (7.4)		
Sustained SVT	6 (22.2)		
Sustained bradycardia			
Sinus/junctional	2 (7.4)		
Second-degree AVB	3 (11.1)		
Third-degree AVB	4 (14.8)		
Total	27 (99.9)		

*PAC denotes premature atrial contractions; SVT, supraventricular tachycardia; and AVB, atrioventricular block.

Table 3.-Patients Referred for Other

Fetal Defect	No. of Patients	Type of CHD*	
2-vessel cord	5		
Omphalocele	5	1 with VSD	
Hydrops	4		
Diaphragmatic hernia	3		
Trisomy 18	2	VSD	
Pleural effusion	2		
Cystic kidney	2		
Cystic lung	2		
Gastroschisis	2		
Teratoma	1	Ebstein's	
Trisomy 21	1	AVSD	
Trisomy 8p	1		
Cystic hygroma	1		

*CHD denotes congenital heart disease; VSD, ventricular septal defect; and AVSD, atrioventricular septal defect

34

1

. . .

Single heart

6 With CHD

Hydrocephalus

Dwarfism

Conjoined

twins

Total

due to severe placental insufficiency related to maternal sickle cell anemia. Deppler tracings of the umbilical artery demonstrated reversed diastolic flow highly suggestive of severe placental insufficiency. The other bradycardic fetus had polysplenia syndrome with an AVSD and severe left ventricular outflow obstruction. An electrocardiogram obtained shortly after term birth demonstrated a slow junctional rhythm. He died at 3 weeks of age and autopsy confirmed the diagnoses of polysplenia syndrome and AVSD.

Three fetuses had second-degree atrioventricular block. One was subsequently found to have l-transposition of the great arteries with ventricular inversion. She developed CHB at 2 weeks of age. One patient's fetus had 2:1 atrioventricular block at 20 and 25 weeks, resolving to normal 1:1 atrioventricular conduction by 30 weeks. He was normal at birth with normal electrocardiogram results and has had no problem. A third fetus, a subsequent pregnancy of the patient just mentioned, had 2:1 atrioventricular block at 20 weeks and was normal at 30 weeks and at birth. The patient has no clinical or serologic evidence of connective tissue disease.

Four fetuses had CHB. Two had severe underlying heart disease with atrial isomerism and AVSD. One pregnancy was electively terminated at 20 weeks. The other child was born at term and died after repair of aortic coarctation and pacemaker implant. The two other fetuses with CHB had otherwise normal hearts. The mothers were clinically normal, but found to have systemic lupus erythematosus by serologic testing. One child was born at term, asymptomatic, and is well at 1 year of age. The other died suddenly in utero at 34 weeks. This fetus also had significant hydrops at 19 weeks. At that time, high maternal SS-B (La) antibody titers were found. Maternal dexamethasone treatment resulted in a dramatic decline in maternal SS-B antibody as well as resolution of fetal hydrops. Numerous scans demonstrated fetal ventricular rates of 50 to 55 per minute.

Thirty-four patients were referred for other defects. Six (18%) had significant CHD. Table 3 lists the defects and associated cardiac findings. Of the 32 patients referred for maternal/fetal drug exposure, no fetus had CHD. Drugs included: lithium carbonate (15), phenytoin (8), tretinoin (4), unknown substance abuse (2), ritodrine (1), birth control pills (1), and valproic acid (1). Thirty-one patients were referred because of obstetrician suspicion of CHD. Each referral was made because of failure to obtain a normal four-chamber fetal cardiac image during routine obstetrical scan. Nine (29%) abnormal fetal hearts were detected in this group. Ten fetal echocardiograms were done for miscellaneous indications (maternal lupus, prior spontaneous fetal death). No abnormalities were found in this group.

A total of 25 fetuses had structural heart disease. The type of CHD, presence or absence of other defects, outcome, method of diagnostic confirmation, and whether the management of the patient was affected by the fetal echocardiographic study are described (Table 4).

The management of the pregnancy was considered affected if the results of fetal echocardiography were considered in continuing or terminating the pregnancy, if transplacental medical management was begun, or if the site of delivery was changed.

Of the 91 patients referred with the indication of family history of CHD, with 3 abnormal results found, there was no alteration of management in any case. Of the 80 patients referred for maternal diabetes, with 4 abnormal results found, management was affected in only 1. The site of delivery was changed to allow delivery of an infant with tetralogy of Fallot and pulmonary atresia at a center with appropriate pediatric cardiovascular resources.

Of the 45 patients referred for fetal dysrhythmia, with 14 significant abnormal results found, management was clearly affected in 7. Five had aggressive medical management with resultant control of SVT; 1 with atrial isomerism, AVSD, and CHB had delivery redirected to an appropriate center; and 1 with CHB secondary to maternal systemic lupus erythematosus received a trial of dexamethasone, with resolution of hydrops and subjective improvement of ventricular contractility.

Of the 34 patients referred for other major defects, with 6 abnormal results found, management was affected by the fetal echocardiogram in 3 patients. One pregnancy was terminated because of the finding of CHD associated with trisomy 18 (the finding of CHD made a major difference in this family's decision). One pregnancy was continued because of finding potentially favorable cardiac anatomy in thoraco-omphalopagus conjoined twins. One fetus with Ebstein's disease had his delivery redirected to a more appropriate center. Although not counted as having management altered, of the 8 fetuses with either omphalocele or diaphragmatic

	Table 4.—Types of CHD*					
Patient No.	CHD	Other Defect	Outcome	Confirmed by		
1	Atrial isomerism, AVSD complete heart block	None	Death	Autopsy†		
2	Ectopic heart, tetralogy of Fallot	Pulmonary aplasia	Death	Autopsy†		
3	Single heart	Conjoined twins	Death	Catheterization†		
4	I-transposition of the great arteries, AVB	None	Well	Catheterization		
5	Large VSD	Trisomy 18	Death	Echocardiography		
6	AVSD	Polysplenia	Death	Autopsy		
7	Ebstein's	None	Well	Echocardiography		
8	AVSD	Trisomy 21	Well	Catheterization		
9	Large atrial septal defect	Holt-Oram	Well	Echocardiography		
10	Large VSD	Trisomy 18	Death	Echocardiography		
11	VSD, valve AS	Pleural effusion	Well	Echocardiography		
12	Large atrial septal defect	Severe small-for- gestational-age	Death	Autopsy		
13	Ebstein's, pulmonary atresia	None	Death	Autopsy†		
14	Tetralogy of Fallot, pulmonary atresia	None	Well	Catheterization†		
15	Large VSD	Omphalocele	Well	Echocardiography†		
16	Valve AS, coarctation	None	Well	Echocardiography		
17	Valve AS, coarctation	None	W'ell	Echocardiography		
18	Hypoplastic left heart, supraventricular tachycardia	None	Fetal d∋ath	t		
19	AVSD	Trisomy 21	Well	Echocardiography		
20	Atrial septal defect .	None	V/eil	Echocardiography		
21	Ebstein's	Teratoma	V∕ell	Echocardiography†		
22	Left ventricle tumor	None	Well	Echocardiography		
23	Atrial isomerism, AVSD, complete heart block	Hydrops	Aborted	†		
24	Large VSD, small left ventricle	Trisomy 18	Aborted	†		
25	Large VSD	None	Not delivered			

*CHD denotes congenital heart disease; AVSD, atrioventricular septal defect; AVB, atrioventricular block; VSD, ventricular septal defect; and AS, aortic stenosis.

†Management of the pregnancy was affected.

hernia, 5 families likely continued the pregnancy because of finding a normal heart.

Of the 31 patients referred because of obstetrician suspicion of CHD, with 9 abnormal results found, management was affected in 4. One fetus with hypoplastic left heart, SVT, and hydrops had no active intervention after finding the hypoplastic left heart, and died in utero. One mother with a fetus with ectopic heart, tetralogy of Fallot, and pulmonary aplasia had cesarean section avoided and vaginally delivered a stillborn infant. One fetus with atrial isomerism, AVSD, CHB, and hydrops was aborted. One fetus with Ebstein's dis-

ease and pulmonary atresia had delivery redirected to an appropriate center.

COMMENT

This series and others, 1,8,16 demonstrate that fetal echocardiography can be a valuable diagnostic tool. Eleven percent significant abnormal results were found in this series.

The largest group of patients was referred because of a family history of CHD. The finding of 3% abnormal results is similar to data reported by others. Although the yield of abnormal results was low in this group, the emotional benefit to the family of finding a normal fetal heart, or of being prepared

for delivery of a baby with an abnormal condition was, in our opinion, a valid reason for the fetal echocardiography.

Five percent of the mothers referred because of insulin-dependent diabetes had babies with significant CHD. This is similar to previous reports. Additionally, because of the risk of placental insufficiency in mothers with diabetes, Doppler evaluation of the umbilical arterial flow may provide important information with regard to fetal well-being. Echocardiography and Doppler evaluation of the fetus of a diabetic mother may be warranted for these reasons.

Of the patients referred for evaluation of fetal dysrhythmia, 53% had a detectable abnormality at the time of our examination. Only 29% had significant dysrhythmia, the rest being clinically insignificant unsustained supraventricular ectopy. Five fetuses with sustained SVT and hydrops were successfully treated and are now healthy children. One of these, initially thought to have idiopathic nonimmune hydrops. was in normal rhythm at the beginning of scan but developed SVT during the scan. This emphasizes the importance of frequent evaluation of any fetus with nonimmune hydrops in diagnosing fetal SVT that might not be detected at any single examination.21

Sustained fetal bradycardia was associated with a high likelihood of serious disease. Only two of nine in this group spontaneously resolved 2:1 atrioventricular block and were normal at birth. Both of these infants were born to the same mother. Detailed serologic testing did not demonstrate any problem in maternal connective tissue. Five of the other seven died either in utero or in the early neonatal period. Identification of the fetus with severe CHD associated with CHB is important, as the overall mortality is high. 22-26 Complete heart block, secondary to maternal connective tissue disease, may also have associated cardiomyopathy that can be improved by treatment to lower maternal antibody levels.27 With further advances in pacing technology, it may become possible to pace the fetus distressed from severe bradycardia long enough to allow it to become viable.28

Thirty-four referrals were made because of other major fetal defects. Six (18%) of these had structural CHD. Table 3 describes the defect and cardiac findings. Of particular significance was the finding that, excluding chromosomal abnormalities, no fetus was found to have a major cardiac defect that adversely affected outcome. The finding of CHD requires amniocentesis or fetal blood sampling as 32% of fetuses with CHD may have an associated chromosomal abnormality.29 The finding of a normal heart in the fetuses with omphalocele or diaphragmatic hernia allowed for a more optimistic outlook to prevail, resulting in continuing, rather than terminating, at least some of these pregnancies.

No abnormalities were found when patients were referred for maternal/fetal drug exposure. The likely occurrence of CHD in this group is small but the possibility of CHD still exists and would probably have been detected in a larger series.

Of those patients referred because of obstetrician suspicion of CHD, 29% of the results were confirmed as abnormal. Each referral was made because of failure to obtain a normal four-chamber view. The importance of including a screening four-chamber cardiac view during ultrasonography of the fetus has been stressed. 16

Five known diagnostic errors occurred. Errors may occur because of the inherent difficulty of imaging a small, moving target and the imaging of the heart and great vessels from a multitude of views. However, these difficulties may actually afford the ultrasonographer the opportunity to view anatomy in striking detail. 30,31 Two errors occurred because of failure to diagnose coarctation of the aorta. Our ability to adequately visualize the aortic and ductal arches in approximately 75% of the studies demonstrates an area of diagnostic weakness, at least in our hands. One patient with l-transposition of the great arteries was incorrectly diagnosed because of failure to correctly determine ventricular and great artery relationships. One patient with valvular aortic stenosis was missed because of failure to appreciate abnormally echodense valve echos (seen in retrospect), and the lack of use of Doppler evaluation of flow in the ascending aorta. No diagnostic error adversely affected management or outcome.

In four patients, unfavorable fetal position and maternal obesity resulted in totally inadequate evaluation. Use of a vaginal probe may help in these instances. We have not had significant experience with this technique.

The effect of the fetal echocardiogram on pregnancy management is important. Simply identifying CHD before birth is not indication enough for these examinations. In this small series of 323 patients, 15 (4.6%) had a clear change in management based on the fetal echocardiographic study. Additional patients may have benefited from these studies in ways more difficult to evaluate objectively. Our experience suggests that the routine use of fetal echocardiography is accurate and will benefit a small but significant number of patients. With advances in infant and fetal surgical and medical treatment, fetal echocardiography will become more important.

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Apnea, Transient Episodes of Bradycardia, and Periodic Breathing in Preterm Infants

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• The occurrence of central apnea of 15 seconds or longer, transient episodes of bradycardia (TEB), and periodic breathing were studied in 66 healthy premature infants when at least 1 week old and between 32 and 36 weeks postconceptual age. Eight-hour cardiorespiratory recordings were visually scanned for the presence of thesee patterns. Central apnea of 15 seconds or longer was seen in almost half of the infants. The TEB were numerous, and the majority were not associated with central apnea; however, all but five of the apnelc episodes that lasted 15 seconds or longer were accompanied by a TEB. Infants spent as much as 40% of their time in periodic breathing. The frequency with which these patterns are seen in healthy premature infants strongly suggests that they are normal findings. Our results do not support the opinion that brief periods of apnea are abnormal when accompanied by a TEB.

(AJDC. 1990;144:54-57)

🚺 ith the advent of continuous cardiorespiratory monitoring of the premature infant, a variety of interesting and sometimes seemingly ominous patterns have been identified in the respiratory and cardiac tracings. Most commonly noted are apnea, transient episodes of bradycardia (TEB), and periodic breathing (PB). 1-11 Before attributing pathologic significance to these patterns, their occurrence in the healthy infant needs to be established. Quantification of these patterns is still incomplete. Many previous reports have been based on small numbers of infants who are at varying ages or have included those who are symptomatic. Few investigators have examined all of these patterns simultaneously in the same infants. The purpose of this study was to define the incidence of central apnea, TEB, and PB in a carefully selected large group of healthy premature

infants between 32 and 36 weeks postconceptional age in a nursery setting.

SUBJECTS AND METHODS

Daily admissions to the intensive and intermediate care nurseries were reviewed to identify potential candidates for the study. Sixty-six consecutive healthy premature infants appropriate for gestational age were selected for the study when they were at least 7 days old and 32 to 36 weeks of postconceptional age. The more mature infants (>34 weeks' gestational age) were frequently discharged by 1 week and were therefore unavailable for study. Gestational age was determined by maternal history if the Dubowitz score12 agreed within 2 weeks. If there was a larger discrepancy, the gestational age that was closest to the 50th percentile for head circumference using the Denver Intrauterine Growth Curve¹³ was assigned. Infants with the following clinical or biochemical findings that might predispose to apnea were excluded: a 5-minute Apgar score below 7, supplemental oxygen for more than 24 hours, assisted ventilation including continuous positive airway pressure, intracranial hemorrhage grades III or IV, sepsis proved by culture, diagnosed medical conditions, anemia (hematocrit value <0.30 after the first week, and biochemical abnormalities of glucose, sodium, or calcium. None of the infants were receiving medications other than the routine administration of vitamins, and they were all fed by nipple or gavage at the time of study.

Cardiorespiratory monitoring (using a Corometrics Neonatal Monitor 512, Corometrics, Wallingford, Conn) was carried out during an 8-hour period starting at approximately 11 PM. This monitoring is part of the routine care in our special care nurseries and is included in the consent process for all hospital admissions. Respirations were recorded by impedance pneumography, and the instantaneous heart rate was calculated from the RR interval of the electrocardiograph. The 8-hour tracings were visually scanned. While obstructive apnea cannot be reliably identified from these tracings, central apneic episodes can be readily recognized.14 Short central apnea of less than 15 seconds in duration was enccuntered so frequently in all of the records that no attempt was made to count all the episodes. All central apnea of 15 seconds or longer was measured and counted. The duration of an apneic episode was measured from the end of the inspiration before the pause to the beginning of the next inspiration. One deflection during a pause was discounted (Fig 1). A TEB was defined as a drop in heart rate below 90 beats per minute. The duration of the TEB was measured from the time the heart rate started to decrease until the maximum point of recovery (Fig 1). Periodic breathing was defined as a visual pattern of repetitive short central pauses separated by bursts of respirations (Fig 2). To qualify, the pauses had to be between 3 and 10 seconds in duration separated by respiratory pauses lasting 20 sec-

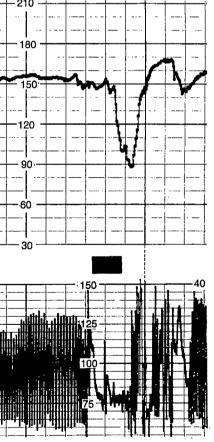


Fig 1.—Central apneic episode of longer than 20 seconds, with one deflection on the lower respiratory tracing associated with a transient episode of bradycardia of longer than 20 seconds, with a peak drop to 90 beats per minute in the upper cardiac tracing. Numbers in the upper segment refer to beats per minute. Each large section equals 1 minute, while each small section represents 10 seconds.

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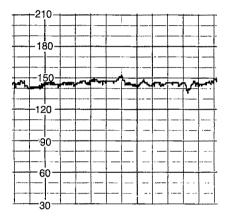
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onds or less, and the pattern had to persist for at least 30 seconds. Regular breathing correlates well with quiet sleep, but irregular breathing occurs in both active sleep and awake states in premature infants. Consequently, it is not possible to report our results in relation to sleep state. When appropriate, χ^2 analysis was used to ascertain differences between variables.

RESULTS

The gestational ages and birth weights of the patient population are shown in Table 1. The infants were all appropriate for gestational age, which is reflected in the mean birth weights. The median gestational age was 32 weeks, and the majority of infants were



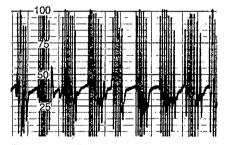


Fig 2.—Periodic breathing with respiratory bursts of 8 to 10 seconds separated by 10-second pauses in the lower segment. Normal heart rate with normal variability at 137 to 152 beats per minute is shown in the upper segment. Measurements are the same as those in Fig 1.

Table 2.—TEB and Apnea Duration*				
Dimetian	Duration of TEB, s (No. [%])			
Duration of Apnea, s	No TEB	<20	≥20	
None-≥15		110 (68)	47 (55)	
15-19	5	34 (21)	35 (41)	
≥20	0	17 (11)	3 (4)	
Total	5	161 (100)	85 (100)	

^{*}TEB indicates transient episodes of bradycardia.

between 32 and 33 weeks of gestation at birth. For evaluation of the results, infants were divided into three groups, those at the median gestational age of 32 weeks, those younger, and those older. The study design required that infants born at shorter gestations be studied at older postnatal ages to achieve comparable postconceptual ages.

Apnea

Approximately half of the infants (53%) had no appeic episodes of 15 seconds or longer. When examined by gestational age, 25%, 44%, and 76% of the infants less than, equal to, and greater than 32 weeks old, respectively, did not demonstrate apneic episodes of 15 seconds or longer (Fig 3). Twenty-five (38%) of the total number of infants had one or more 15- to 19-second apnea, and in 10 infants (15%), the duration was 20 seconds or longer. Four of these 10 infants (6% of the total population) had two or more episodes of apnea of this duration. Four infants had appea that lasted both 15 to 19 seconds and 20 seconds or longer and are included in both categories in Fig 3. A sharp drop in the incidence of longer apnea occurred in infants 33 weeks old and older at birth.

There was a total of 94 individual apneic episodes of 15 seconds or longer. Twenty of the 94 episodes lasted 20 seconds or longer, and 5 of these were between 30 and 40 seconds in duration. Our nursery protocol dictates observation of the infant at 20 seconds, skin stimulation at 30 seconds (unless clinical signs of cyanosis or pallor are present earlier), and ventilation with a mask and bag if there is no response by 40 seconds. The 5 prolonged apneic episodes reported herein responded to skin stimulation, and none needed intervention by mask and bag ventilation.

Lower 1-minute Apgar scores were associated with more frequent long apneic episodes after the first week of life. Although all of the infants' 5-minute Apgar scores were above 6 by study design, 6 (33%) of the 18 with a 1-minute score of 6 or less had apnea of 20 seconds or longer as compared with 4 (8%) of 48 with 1-minute scores of 7 or above (P < .05).

		Mean	±SD
Gestational Age, wk	No. of Infants	Birth Weight, g	Postnatal Age, d
28	3	1233±60	28±3
29	1	1480	21
30	2	1340 ± 57	18±3
31	10	1591 ± 192	16±8
32	25	1696 ± 279	11 ± 5
33	10	1724 ± 227	10±4
34	14	1889 ± 194	8±2
35	1	2050	7

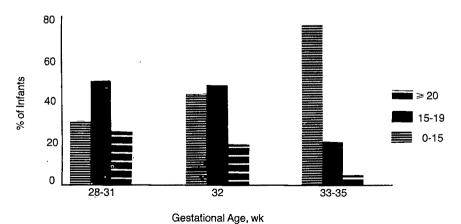


Fig 3.—Duration of apneic episodes (in seconds) as a function of gestational age. Ordinate indicates the percentage of infants exhibiting apneic episodes of various durations.

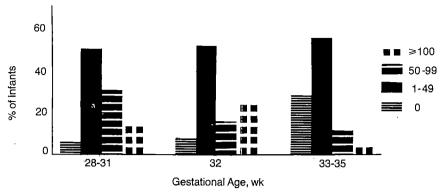


Fig 4. — Duration of periodic breathing (in minutes per 8-hour tracing) as a function of gestational age. Ordinate indicates the percentage of infants exhibiting periodic breathing of various durations.

TEB

Decreases in heart rate to less than 90 beats per minute were a common occurrence. Forty-five infants (68%) showed TEB, with a range of 1 to 18 episodes and a mean of 2.6 in the 8-hour tracing. One third (85) of the total 246 TEB lasted for 20 seconds or more, while two thirds (161) were brief, lasting for less than 20 seconds (Table 2). Sixty-eight percent of these brief TEB occurred without evidence of central apnea of 15 seconds or longer. When TEB of 20 seconds or longer were considered, 55% were still not associated with central apnea of 15 seconds or longer. While the majority of TEB did not accompany a long apneic episode, all but 5 of these apneic episodes of 15 seconds or longer were accompanied by a TEB.

PΒ

Eight infants had no PB during the approximately 480 minutes of recording, 37 exhibited PB for 1 to 49 minutes (up to 10%) of the recording time, 12 had PB between 50 and 99 minutes (10% to 20%), while 9 infants breathed periodically for more than 100 minutes (>20%) (Fig 4). The mean number of minutes of PB was 47.5, with a large SD of 45.2 minutes and a range of 2 to 195 minutes. The mean percentage of total recording time spent in periodic breathing was 9.92, and the median percentage for those infants exhibiting periodic breathing was 8.90. As can be seen in Fig 4, there was a tendency for less mature infants, those younger than 33 weeks of age, to spend more time

breathing periodically. Of the 9 infants who spent more than 20% of their time in PB, none exhibited apnea between 15 and 19 seconds, and only 1 had apnea of 20 seconds or longer, suggesting that PB does not predispose to apnea in healthy premature infants. This is also supported by the observation that only one fifth of the 94 episodes of apnea 15 seconds or longer described above occurred during PB.

COMMENT

All of the patterns described herein were common in healthy premature infants. Central apnea of 15 seconds or longer was seen in almost half of the infants. The TEB were numerous and most were not associated with central apnea. Infants spent as much as 40% of the recording time in PB. There was considerable variation among individual infants in all the parameters. The incidence of apnea and PB decreased after 32 weeks of gestational age.

Comparison of our results with previous reports is difficult due to variance in both study populations and methods. Investigators who studied premature infants agree that episodes of apnea 20 seconds or longer are seen in healthy infants, that the incidence of apneic episodes decreases with both increasing gestational and chronologic ages, and that the variability among infants is large. 4,8-16 Our data support these conclusions. Daily et al4 reported an incidence of 30% for apneic episodes of 20 seconds or longer in all premature infants after the first week. This figure is twice that found in the present study but included symptomatic as well as healthy infants.

While prolonged apnea occurred in 15% of our infants, repetitive episodes of this duration were seen in only 6%. Thus, within this healthy group, 6% of the infants would be classified as having clinically significant apnea using our current definition of repetitive prolonged episodes. Of interest, a low 1-minute Apgar score was associated with a significant increase in prolonged apnea after the first week of life even though the infants had no other clinical findings.

The TEB were common, occurring in 45 (68%) of the 66 recordings. This heart rate pattern was described in the healthy infant as early as 1963¹⁵ and can be equated with the benign v-shaped or type 1 dips of the fetal heart rate. ¹⁶ Several previous studies of TEB in conjunction with apnea as well as the present report found this pattern to increase in incidence with increasing duration of the apnea and to decrease with increasing gestational and chronologic age. ^{9,17-19}

We found that the majority of TEB occurred without central apnea. Smith and Milner, 20 using impedance pneumography and observation, also reported that many TEB were not associated with central apnea but rather with changes in respiratory pattern and somatic movement. In both Smith and Milner's study and ours, some of these episodes may have represented obstructive apnea. The TEB have been reported as especially common during obstructive apneic episodes.17,21,22 Obstructive apneic episodes are difficult to identify with the usual clinical recording method of impedance pneumography. Using special techniques, Thach and Stark²³ reported that between one third and half of all apneic episodes were mixed and obstructive rather than central. Currently, however, there is controversy as to whether some of the recorded phenomena represent body movements rather than true apnea.24

Although PB is reported as common, especially in the least mature infants, figures for incidence or duration are rarely included. Curzi-Dascalova and Christova-Gueorguieva reported that infants less than 36 weeks of gestational age breathed periodically 8.3% of sleep time, a figure in close agreement with our own. Results of our study indicate that the percentage of time spent breathing periodically by healthy pre-

term infants may be large and is certainly highly variable.

While the frequency with which these cardiorespiratory patterns are seen in the healthy infant strongly suggests that they are normal, investigation of associated physiologic changes is needed to confirm this. The brief episodes of bradycardia are responses to numerous internal and external stimuli probably mediated through the vagus.27 Although the majority are not initiated by hypoxemia,27,28 TEB can be influenced by the level of oxygenation of the infant.29 For example, the reflex TEB associated with sectioning of the tracheobronchial tree can be modified or eliminated by preoxygenation.³⁰ The effects of apnea and TEB on cerebral blood flow have been reported recently in very-low-birth-weight infants by Perlman and Volpe.31 Decreases were seen in both systolic and diastolic blood flow when the TEB dropped below 80 beats per minute, suggesting that deep dips, especially if prolonged or repetitive, may have pathologic consequences.

Oxygen levels during periodic breathing are lower than those during regular breathing but are still well within normal levels in healthy infants. ^{6,32} Certainly. PB can be induced by relative hypoxia and relieved by increasing ambient oxygen. ^{6,32} In infants with cardiorespiratory disease and little reserve, periodic breathing may be an indication of hypoxia, ³² but the clinical implications of this finding in healthy preterm infants are unknown.

A relationship with sequelae on follow-up would also help define the limits between normal and abnormal cardiorespiratory findings. Surprisingly little information is available. Butcher-Puech et al³⁴ showed a relationship between obstructive apnea in the nursery, intraventricular hemorrhage, positive pressure ventilation, and abnormal neurodevelopment at 1 year; however, these findings are not necessarily relevant for healthy infants. The opinion expressed in the recent National Institutes of Health (Bethesda, Md) consensus report was that apnea in the nursery has little influence on later performance.35

In 1978, the American Academy of Pediatrics Task Force on Apnea defined clinically significant apnea as episodes of 20 seconds or longer or briefer spells associated with a TEB.36 The results of our study do not support the opinion that brief episodes of apnea are abnormal when associated with TEB. Apnea of 15 to 19 seconds associated with drops in heart rate are common in healthy preterm infants and this association should not be considered an indication for treatment or long-term cardiorespiratory monitoring. Treatment to eradicate a normal finding, such as TEB or PB, can be risky.29 It seems appropriate for us to remember that administration of oxygen, which successfully treated periodic breathing in the healthy premature infant, was at least partially responsible for the epidemic of retrolental fibroplasia that occurred 40 years ago. 37

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Serial Abuse in Children Who Are Shaken

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· Serious injury can occur to children who are shaken, especially if the shaking Is repeated or part of a pattern of abuse. Serial abuse in connection with children who are shaken and their siblings has important therapeutic and legal ramifications. From an ongoing study of child abuse and head trauma, 12 of 24 victims of shaking that resulted in intracranial injury were identified who had coexisting evidence of direct external trauma. Seventeen children (71%) had evidence of prior abuse, neglect, or both, including 8 who had multiple intracranial hemorrhages. Of the 21 families represented, 9 had more than one child, 3 (3%) of which had several siblings who had been victims of child abuse. Shaking of children usually is not an isolated event, as it frequently has been preceded by other types of abuse.

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The signs associated with an episode of repetitive and violent shaking (retinal hemorrhages or intracranial hemorrhages) were described in 1946.1 In 1971, Guthkelch² first implied that such injuries resulted from "whiplash" forces.2 Shortly thereafter, Caffey3,4 (in 1972 and 1974) further described repeated shaking as a cause of retinal hemorrhages and intracranial injuries without visible signs of external trauma. The shaken baby syndrome (SBS) usually implies the application of repeated forces over one or more episodes. Such repetitive insult suggests that the perpetrator has less self-control or more rage, with the possibility of prior abuse for the index child or siblings.

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The recidivism rate for all child abuse in Iowa is approximately 33%, which corresponds to the national frequency of recidivism.6 The prospect of further injury to a shaken child and to other siblings has serious medical and legal ramifications. Old and new intracranial injuries, 7,8 optic nerve sheath injuries, 9 and sibling deaths10 have been described. To the best of our knowledge, no systematic documentation of serial abuse in shaken children and their siblings has been undertaken. Our study was intended to examine the rate of recidivism for shaking and to determine if prior abuse occurred with extracranial injuries and for siblings.

SUBJECTS AND METHODS

All children seen between July 1, 1984, and December 31, 1988, at The University of Iowa Hospitals and Clinics, Iowa City, with a diagnosis of SBS (confirmed by a multidisciplinary team of child abuse professionals) have been included in an ongoing study of head trauma and child abuse. Additionally, all children with SBS were included from among those examined in the Iowa Medical Examiner's Office, Des Moines, during the same period. We determined whether other siblings were abused and examined their medical records and imaging studies for evidence that they had been shaken. Information about abused siblings was obtained by intensive child protective service and prosecutor investigations in each instance. At least one of us (R.A., W.S., or T.B.) participated in the medical and legal aspects of each case. Evaluation consisted of the following: physical examination; skull roentgenograms; a skeletal survey; computed tomography (CT), magnetic resonance imaging (MRI), or both; and an autopsy (when applicable). The CT, MRI, and autopsy findings were specifically examined for evidence of intracranial hemorrhage of differing ages. The participation of personnel from Iowa Child Protective Services provided access to previous reports of child abuse, the results of current investigations, old medical records, and the status of other children in the family.

The ages of the intracranial injuries were dated by evaluation using CT or MRI. Signa intensities of CT and T₂-weighted MRI images were compared with known patterns of hemoglobin breakdown. ^{11,12} Autopsy findings, as provided by a forensic pathologist, supplemented the data. Estimates of the dates for bruises were made by their color and for fractures by their degree of callus formation. ¹⁴

RESULTS

As displayed in Table 1, 12 of the 24 patients sustained external head trauma in addition to being shaken. Although the SBS has been defined by the absence of visible external trauma, 3,4 we applied stricter criteria to distinguish instances of shaking only. These criteria included absence of evidence of direct external trauma as determined by the following: physical examination; roentgenograms; CT, MRI, or both; and autopsy findings. Seventy-one percent (17) of all patients (58% of those shaken alone) had evidence of prior abuse, neglect, or both. Previous traumatic injuries (ie, intracranial hemorrhages of different ages or prior extracranial abuse) were more common than neglect; no instances of sexual abuse were found. Shaking was a multiple occurrence for 25% of those without signs of direct cranial impact injuries (33% of all cases). No significant differences in frequency or types of prior abuse or neglect were found between the group that had only been shaken and those who were shaken and suffered injuries of cranial impact.

Most patients (57%) came from families in which no other siblings were present (Table 2). In one instance, an earlier sibling had been given up for adoption at birth; the other patients were first-borns and only children. For families with two or more children, no evidence of prior abuse or neglect was found if the index patient had a combination of shaking and impact injuries. Of the families

Table 1.—Abuse or Neglect in the Same Child			
Characteristics	Shaking and Direct Blow(s)	Shaking Only	
No. of patients	12	12	
Patients with evidence of the following: Prior abuse, neglect, or both*	10	7	
Intracranial hemorrhages of different ages	5	3	
Prior extracranial abuse	4 definite and 1 possible	3	
Neglect or failure to thrive	2	2	

^{*}Some patients had more than one type of prior abuse or neglect.

Table 2.—Abuse or Neglect Within the Family					
Shaking and Characteristics Direct Blow(s) Shaking Onl					
No. of families	12	9*			
Families with other siblings Siblings with SBS	4 0	5 3			
Siblings with other abuse or neglect	0	. 1			

^{*}Two fami ies each had three siblings: there were three children with shaken baby syndrome (SBS) in one family, and two of three had SBS in the other family.

with more than one child in which one child had received shaking injuries alone, three (60%) of five also had another abused or neglected child. In two of these families, siblings also suffered shaking injuries without detectable external head trauma. In the other family, a child abuse report was substantiated for neglect of a sibling 6 years before the death of the patient.

COMMENT

Shaking was associated frequently with other instances of abuse. For 50% (12) of the children, shaking was directly accompanied by some form of external cranial trauma. The types of injuries were similar to those seen by Sinal and Ball¹⁰ (1987), who found 17 patients with SBS among 24 children with head trauma caused by abuse, although they did not use MRI as a diagnostic aid (one of our patients was classified as having had direct trauma based on MRI findings alone).8 Prior abuse or neglect of the patient was common (71%). Among all patients, 33% had been previously shaken, corresponding to the 33% recidivism rate reported for child abuse in general (but less than the 71% rate of prior abuse or neglect found in the patients). Usually, the patient was the only child in the family. The risk of abuse to any subsequent siblings may be approximated by the finding that in 33% of families with more than one child, two or more siblings experienced abuse or neglect. Because all previous medical records were not routinely reviewed on the siblings in each case and not all abuse is reported, the percentage of abused siblings might be an underestimate. In two families, more than one child was shaken sufficiently to cause the death of one sibling and injury in the other(s).

The risk of subsequent abuse is likely an underestimate. We evaluated only those patients presenting with sufficient symptoms for medical recognition. Subacute shaking that caused concussion or more subtle long-term effects in these children or their siblings may have gone undetected.4 An increase in the use of MRI has helped detect old and new intracranial injuries and has aided in the recognition of subtle instances of repetitive shaking. 8,15 Children who died of an acute assault may have suffered future additional abusive intracranial injury had they survived. Social service and legal intervention in some cases may have attenuated the risk to other siblings, thereby blunting a possible repetition of abusive shaking behavior. Although the risk of subsequent abuse under the same circumstances is an important assessment, failure to intervene is not ethically acceptable.

The importance of establishing repetitive abuse has indirect and direct legal implications. Indirectly, the risk of further abuse to the patient or to other siblings must be weighed along with the seriousness of such injuries when deciding placement issues and prognosis for reunification of the family. Shaking children rather than hitting them may be misperceived by parents as less "abusive,"2 despite data that indicate that shaking alone in comparison with shaking and direct cranial trauma has an equal fatality rate (R.A., Y.S., W.S., and T.B., unpublished data, 1989) and that shaking often results in significant morbidity.16 The fact that shaken children, and possibly their siblings, often have been previously abused should correct the notion that shaking is an isolated and somewhat "unintentional" event. Such misperception by judges or juries may be partly responsible for the ultimate verdict of involuntary manslaughter. From the perspective of the protection of the child or the criminal prosecution of the abuser, it is not as important to distinguish the precise mechanism of injury as it is to determine whether the event was accidental or nonaccidental. Pediatricians should not be deterred from testifying just because the cause of the nonaccidental injury is not entirely clear.

More direct legal implications were illustrated by two children who died of SBS, for whom findings of repetitive abuse resulted in first-degree murder convictions. The first, a 71/2-month-old male infant, had bilateral retinal hemorrhages and subdural hematomas diagnosed on CT, MRI, and at autopsy. Two 8-week-old twin half-brothers in another state had been previously shaken, resulting in subarachnoid hemorrhages (one child had old and new hemorrhages on CT). The biologic father of all three children was convicted of first-degree murder based on prior knowledge, ie, he knew the effects of shaking after previously abusing his two other children.

The second child, a 6-week-old female infant, had fractures of three ribs and an ankle in three different stages of healing, bilateral retinal hemorrhages, massive bilateral subdural hematomas, and intraparenchymal brain shearing damage at gray-and-white matter inter-

faces. The pattern of repetitive physical abuse and the acute assault, warranted charges of felony child endangerment. In the course of committing this abuse, the father fatally shook his child. Although no suggestion was made that this action was premeditated, killing in the course of a felony (felony murder) is first-degree murder in Iowa. Thus, in one instance, serial abuse of the siblings resulted in the maximum conviction,

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while in the second case it was based on serial abuse of the same child.

Shaking a child represents an imminent risk for acute injury. Frequently it is not an isolated event and poses substantial risks for further abuse of the child and his or her siblings. Based on a high index of suspicion for possible child abuse, a diagnosis of shaking should lead to intensive efforts to identify concurrent and previous abuse of the pa-

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tient (eg, skeletal survey, CT, and MRI) and of the siblings. Recognition of serial abuse is essential in directing appropriate therapeutic interventions to reduce the risk to children and in addressing appropriate criminal sanctions.

James Metcalf, JD, Jerry Partridge, JD, and Barbara Edmondson, JD, contributed to the case studies and legal interpretations of the importance of repetitive shaking. Kelly Lindsey, MD, provided technical assistance, and Rebecca Fitch helped prepare the manuscript.

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Correction

Incorrect Data.—In the article "Risk Factors for Infant Botulism in the United States," published in the July 1989 issue of *AJDC* (1989;143:828-832), an error appeared because of incorrect information supplied by the author. On page 831, the first complete sentence of the middle column should begin, "The 32 (47%) infants who had at least one BM every 3 days..."

Major Congenital Neurologic Malformations

A 17-Year Survey

LTC Thomas E. Wiswell, MC, USA; Capt Deborah J. Tuttle, MC, USAF; CPT Ralph S. Northam, MC, USA; CPT Gary R. Simonds, MC, USA

• We present characteristics of four major congenital neurologic malformations-anencephaly, spina bifida, encephaloceles, and hydrocephalus-from a population of 763 364 live-born and stillborn infants born from 1971 through 1987. During the 17-year study period, 275 infants had an encephaly (0.36 per 1000 total births), 526 had spina bifida (0.69 per 1000 total births), 112 had encephaloceles (0.15 per 1000 total births), and 370 had hydrocephalus (0.48 per 1000 total births). There was a female preponderance of infants with anencephaly, spina bifida, and encephaloceles, while males predominated among those with hydrocephalus. We found declining incidences of anencephaly, spina bifida, and encephaloceles only among white females. Black infants were significantly less likely than white infants or infants of other races to have spina bifida. Twenty percent of Infants with anencephaly had congenital anomalies unrelated to the primary defect, as did 40% with encephaloceles, 37% with hydrocephalus, and 22% with spina bifida. Because the racial background of the patient population closely resembles that of the United States as a whole, the features of the malformations described may reflect those of the country.

(AJDC. 1990;144:61-67)

M ajor congenital neurologic malformations are common defects that cause morbidity and mortality among newborns. Several of these anomalies, including hydrocephalus and the neural tube defects (anencephaly, spina bifida,

and encephaloceles), are reported to have been declining in incidence over the past two decades. 1-24 Although these reports have been reported worldwide, the reported declines of these anomalies have been particularly notable in the Kingdom. 6-8,10,20-22 However. United many authors have found stable or even increasing incidences of these four anomalies during the same period.* In addition, an apparent East-to-West declining gradient in the prevalence of neural tube defects has been described; the highest rates are in the British Isles and the lowest in Japan, with North America in between (to wit, more affected infants on the East Coast and fewer on the West Coast). 1,4,27,36-39 Furthermore, conflicting data exist regarding racial, seasonal, and sexual variations in the incidences of these malformations. 1-4,27,31,33,35,37-52 The information from studies in the United States is equally confusing. †

Why should we be interested in retrospective analyses of population-based series of major central nervous system (CNS) malformations? Such studies may provide useful information on time trends, on the origin or cause of the defects, and on goals for health care measures, such as the following: (1) planning and implementing health care services for the survivors; (2) prenatal screening and elective termination of pregnancy; (3) potential use of anencephalic patients' organs for transplants; and (4) evaluation of these programs.

We designed this investigation to examine characteristics of major congenital neurologic malformations with the following purposes: to evaluate the incidences of these deformities, as well as

seasonal, racial, and sexual aspects; to ascertain associated congenital malformations; to study geographic differences; and to describe other pertinent findings. Our study population had racial and socioeconomic characteristics similar to those of United States population as a whole. Thus, we believe it is reasonable that our findings may generally reflect those of the nation.

METHODS

Our source of information was the US Army Patient Administration and Biostatistics Activity at Fort Sam Houston, Tex. We examined selected data from all live-born and stillborn infants born in US Army hospitals worldwide from January 1, 1971, through December 31, 1987, with the following diagnoses: (1) anencephaly; (2) spina bifida, excluding spina bifida occulta and meningoceles; (3) encephaloceles; and (4) congenital hydrocephalus diagnosed during the first month of life and unassociated with spina bifida, meningitis, or an intracranial hemorrhage. Infants with anencephaly and another neural tube defect were classified as having anencephaly, while those with encephaloceles and spina bifida were classified as having encephaloceles.

The available information for each child included the hospital of birth, sex, race, the date of admission, all diagnoses and procedures, and outcome, including whether the child died or was transferred to another facility. This information was initially noted by the child's primary physician at the time of disposition. Medical records personnel subsequently transcribed the data. Following disposition, an attending physician reviewed and verified the information before its being sent to Patient Administration and Biostatistics for storage. This information was additionally substantiated by reviewing separate databases cept at several of the hospitals.

The CNS malformations under consideration are generally appreciated during the neonatal period. Because information from all medical records in the army is collected by

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The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army, the Department of the Air Force, or the Department of Defense.

^{*3, 5, 6, 14, 15, 18-20, 23, 25-35.} †2-4, 23, 24, 27, 30, 35, 36, 38, 50-52.

Patient Administration and Biostatistics, we believe there is complete identification of cases. However, a few cases of congenital hydrocephalus may not have become apparent until after the first month of life. In addition, some associated congenital anomalies may not have been noted, particularly among stillborn infants. We use the term incidence to represent the number of live-born and stillborn infants delivered at 20 weeks or longer gestation with one of the four CNS malformations per unit of population over a specific period.⁵³ In this investigation, we examined the number of affected infants per 100 000 total births (live births plus stillbirths) per year.

To evaluate geographic differences, we examined infants born in army facilities within five geographic zones ranging from Europe (Belgium, Germany, and Italy) to the Pacific Rim (South Korea and Hawaii). The three racial categories were white, black, and "other." The other category consisted of approximately 90% Hispanic and 10% Oriental infants.

Data were evaluated for significance with linear regression, analysis of variance, χ^2 analysis, and the χ^2 test for linear trends. We used the method of Walter and Elwood to examine for seasonal variations. $P \le .05$ was considered statistically significant.

RESULTS

During the 17-year study period, there were 763 364 total births (51.05% male and 73.33% white, 17.35% black, and 9.32% other). Of these infants, 4951 (0.65%) were stillborn. A total of 1283 infants (0.168%) had one of the four major neurologic malformations: 526 had spina bifida, 370 had hydrocephalus, 275 had an encephaly, and 112 had encephaloceles. Of the 1283 affected infants, 175 were stillborn. The frequency of the CNS defects among stillborn infants was 3.53% (175/4951), while among liveborn infants it was 0.145% (1098/758 413), a 24-fold difference. Characteristics of affected newborns are presented in the Table. Overall female preponderance for an encephaly (63.6%, P < .0001), spina bifida (54.0%, P = .0179), and encephaloceles (56.3%, P=.1246) was present, while males predominated among infants with hydrocephalus (63.2%, P<.0001). The female preponderance for an encephaly was statistically significant among white (P < .0001)and black (P=.0468) infants, but not among infants of other races. Spina bifida and encephaloceles were more common in white females (P = .0109 and

Characteristics of 1283 Children With Major Congenital Neurologic Malformations				
Feature	Anencephaly	Spina Bifida	Encephaloceles	Hydrocephalus
No. of affected infants	275	526	112	370
No. (%) of female infants	175 (63.6)	284 (54.0)	63 (56.3)	136 (36.8)
No. (%) of liveborn infants	162 (58.9)	508 (96.8)	106 (94.6)	331 (89.5)
No. (%) of stillborn infants	113 (41.1)	17 (3.2)	6 (5.4)	39 (10.5)
No. (%) of live-born premature infants	71 (43.8)	40 (7.8)	25 (23.6)	42 (12.7)
No. (%) with other congenital malformations	55 (20.0)	118 (22.4)	45 (40.2)	138 (37.3)
No. (%) live-born who died during initia! hospitalization	162 (100)	71 (13.9)	19 (17.9)	55 (16.6)
Frequency of birth per live-born and stillborn	1/2881	1/1451	1/6816	1/2063
Incidence per 100 000 births (live-born and stillborn)/y	36.02	68.91	14.67	48.47

.0366, respectively), but not among females of black or other races. Hydrocephalus was significantly more common (P<.01) among males of all racial categories.

A high percentage of anencephalic infants were stillborn (41.1%) or born prematurely (43.8% of live-born anencephalic infants). The median age of death of live-born infants with anencephaly was 1 day. However, several anencephalic infants survived between 2 and 4 weeks. No anencephalic newborns were placed on life-support systems to prolong survival pending possible organ donation.

The yearly incidences of each of the four defects are presented in Figs 1 and 2. Among infants with anencephaly, there was a statistically significant overall decline of 2.1% per year during the 17-year period (P=.012). However, this decline was found only among female infants (2.94% per year, P=.0019).

There were similar overall findings among infants with spina bifida and encephaloceles. For these defects, the decreases were seen again only among female infants: spina bifida, 2.19% per year (P=.045) and encephaloceles, 3.30% per year (P=.019). There was little variation over time in the occurrence of congenital hydrocephalus among both male and female infants.

The incidences of the individual CNS malformations differed based on race

and sex. No significant racial differences were noted for anencephaly, encephaloceles, or hydrocephalus. However, black infants of both sexes were significantly less likely to have spina bifida than white infants (P < .0001) and infants of other races (P<.0001). Although a decline in the incidence of anencephaly was seen among females of all races, it was statistically significant only among white females (P = .0028). Furthermore, the decreases in the incidences of both spina bifida and encephaloceles occurred solely among white females. The incidence of hydrocephalus, however, was stable among females of all races during the 17 years of the investigation. No significant changes occurred in the incidence rates of any of the four malformations among males of any race.

To ascertain geographic differences, we studied five separate regions: Europe (hospitals in Belgium, Germany, and Italy): East Coast (facilities from New York State to Georgia): Midwest (institutions from Kentucky to Colorado); West Coast (California to Alaska); and the Pacific (Hawaii and Korea). The overall incidence of each defect for the five regions is shown in Fig 3. No significant differences were noted in the occurrence of anencephaly or spina bifida. However, hydrocephalus was significantly more common (P<.01) in the Pacific region compared with all other areas, while encephaloceles were signif-

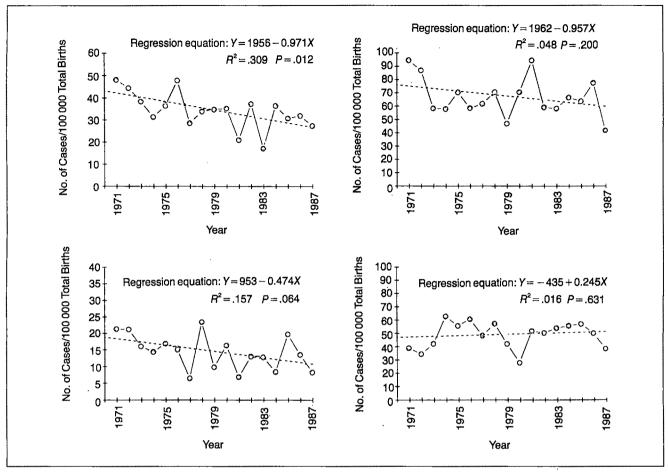


Fig 1.—Graphs of the time trends for four major congenital neurologic malformations—top left, anencephaly; top right, spina bifida; bottom left, encephaloceles; and bottom right, hydrocephalus—from 1971 through 1987. The overall decrease was significant only for anencephaly. Light dotted lines are regression lines.

icantly less common in this region (P<.01) compared with Europe, the East Coast, and the Midwest.

Finally, there were no geographic variations with time in the incidences of any of the four malformations (ie, changes in one area not seen in others) during the study period. The number of affected infants born during each month of the year is shown in Fig 4. No statistically significant seasonal variations were noted for any of the defects.

Twenty percent of newborns with anencephaly had congenital anomalies unrelated to the primary defect, as did 40% of those with encephaloceles, 37% of hydrocephalic infants, and 22% of those with spina bifida. Seven of the 162 live-born anencephalic infants had cardiac defects. However, we do not know how many of the remaining 155 infants were closely examined before or after death for such defects. Thus, we were unable to determine how many liveborn anencephalic newborns could have been considered for potential organ donation. Eleven infants had an encephaly and spina bifida, while 10 had concomitant encephaloceles and spina bifida. The most frequently found defects among infants with spina bifida were gastrointestinal, genitourinary, and cardiac malformations, while multiple anomalies, cleft lip and palate, and other neural tube defects were often found among anencephalic infants. Infants with encephaloceles frequently had multiple anomalies, cleft lip and palate, and limb defects, while the most common defects among hydrocephalic infants were tracheoesophageal fistula, and genitourinary, cardiac, and multiple anomalies.

COMMENT

We have described characteristics of four major congenital neurologic malformations in a large population of infants born during a 17-year period. The racial background of these infants is virtually identical to that of infants born in the United States as a whole. The overall incidences of the four defects were similar to those described in the United States by the Birth Defects Monitoring Program. However, the latter report does not describe differences based on sex or racial backgrounds.

The incidences of neural tube defects vary widely. The neural tube defects are most common among infants born in the British Isles, with as many as 300 to 600 patients with spina bifida or anencephaly born annually per 100 000 live births. 17,10,52,37 With the exception of India,40 most countries report incidences considerably lower than those of the United Kingdom.‡ The most common

^{‡2, 3, 5, 11, 16, 18, 19, 23-27, 29-31, 33-36, 41, 42, 44, 45, 48, 50, 59.}

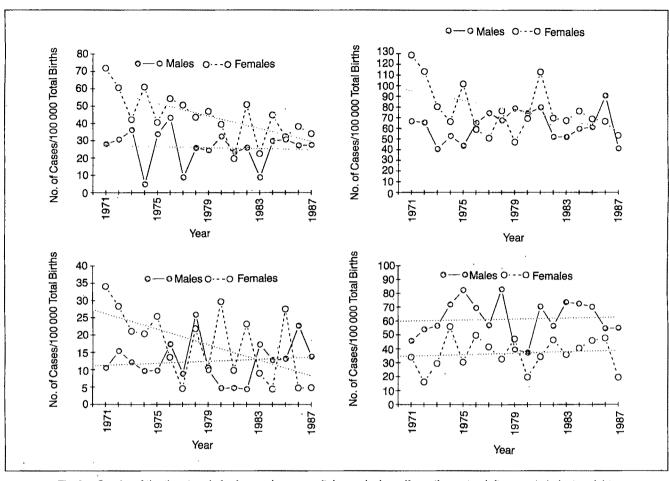


Fig 2.—Graphs of the time trends for four major congenital neurologic malformations—top left, anencephaly; top right, spina bifida; bottom left, encephaloceles; and bottom right, hydrocephalus—from 1971 through 1987 based on the sex of the affected infants. The declining incidences were statistically significant for female infants for anencephaly, spina bifida, and encephaloceles. Light dotted lines are regression lines.

estimate is that both spina bifida and anencephaly occur in approximately 1 per 1000 (100 per 100000) total births. 1,5,80,38 However, we found the incidences of these malformations to be substantially lower (spina bifida, 68.91 per 100 000, and anencephaly, 36.02 per 100 000). Several other recent American studies have described rates similar to our rates. 2,3,23,27,35,36,50 The low prevalence of encephaloceles in the study population (14.67 per 100 000) is comparable with those of other reports. 1,11,19,23,27,30-32,48 In addition, we found hydrocephalus to occur in 48.47 per 100 000 total births, a rate similar to those of other major American studies.3,22,52 We believe the incidence figures for the four malformations in the study population may accurately reflect those of the entire country.

During the past two decades, declines in the birth frequencies of anencephaly

and spina bifida have been noted in many countries. In particular, remarkable decreases in the occurrence of these anomalies have been noted in the British Isles. 6,7,10,20,22 By contrast, multiple investigators have failed to find any significant declines in the frequency rates of one or both of the defects during the same period. Furthermore, there is no evidence for a decline in the prevalence of encephaloceles. 19,28,30 Finally, Lorber and Ward⁷ and Pietrzyk et al¹⁸ have described declines in the incidence of hydrocephalus, while others have found either no change 19,23,52 or increases^{31,34} in this entity's occurrence.

We did not find significant changes in the frequencies of any of the four defects among male and nonwhite female infants. Among white females, however, the incidences of the three neural tube defects decreased during the 17-year period. Windham and Edmonds² found rates of neural tube defects to be declining among both sexes in the United States, particularly among stillborn females. We found similar declining frequency rates of the neural tube defects among both live-born and stillborn white females. Windham and Edmonds did not specifically address changes among infants of different races. To date and to our knowledge, no other investigators have addressed the issue of changes in prevalence of the defects based on sexual and racial differences.

Numerous hypotheses 18,12,37 have been suggested to explain the recent declines in the incidences of neural tube defects that have been noted. The theories include the effects of antenatal screening and elective termination of pregnancy, improved nutrition (including vitamin supplementation), changing age and

^{\$2, 3, 6, 7, 9-11, 13-17, 22-26.} ||3, 5, 14, 15, 20, 27, 28, 30-33, 35.

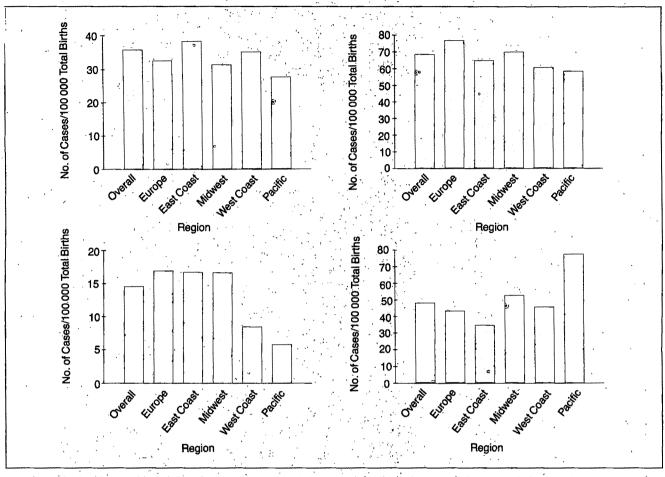


Fig 3.—Geographic variations for four major congenital neurologic malformations—top left, anencephaly; top right, spina bifida; bottom left, encephaloceles; and bottom right, hydrocephalus—for five geographic areas during the period 1971 through 1987. The only significant differences were in the Pacific region, ie, a lower incidence of encephaloceles and a higher incidence of hydrocephalus.

parity distributions in the population, alterations in drinking water composition, and drug use during pregnancy. Since the early 1980s, virtually all theraboutic abortions among pregnant army-associated women (either in the army themselves or dependents of army personnel) have been performed in nongovernment hospitals. Thus, we are unable to assess the influence of prenatal screening and subsequent pregnancy termination on the rates of neural tube defects in our population. We have only noted a significant decline in the incidence of neural tube defects among white females. We are unable to propose any particular factor(s) that could influence declines in neural tube defects sclely in this group.

Since the 1930s, at least some parts of the United States and Canada have experienced a long-term decline in the prevalence of spina bifida and anencephaly. 8,12,24,37 Similar long-term declines have been noted in Sweden, the Netherlands, and Germany. However, long-term decreases in the occurrence of neural tube defects were not noted in reports from Australia or Utah. Complete army-wide medical data before 1971 are unavailable, and we are unable to substantiate whether such long-term secular trends have occurred in our population.

Several studies have found no female predominance in the incidence of one or more of the neural tube defects. 51,283,28,47,48,50 Our findings substantiate the generally accepted belief that more females than males are afflicted with all three neural tube defects. 13,28,57,41 However, we did not find a female preponderance in black infants for spina bifida or encephaloceles.

Conflicting data have been reported regarding ethnic variation in the frequency of major congenital neurologic defects present at birth. 1-4,35,57-42,48,50 We have found differences only in the incidence of spina bifida; black infants (both male and female) are less likely to have spina bifida than white infants or infants of other races.

A few investigators have reported seasonal peaks in the occurrence of spina bifida and anencephaly. \$1,39,42,44\$ Others, however, have not found such variations for these malformations. 1,8,18,27,31,33,45 or for hydrocephalus and encephaloceles. 19,31 We did not find any significant seasonal trends among the study population for any of the four malformations.

An East-to-West declining gradient of neural tube defects across the United States has been claimed.^{1,4,27,58-39} We only

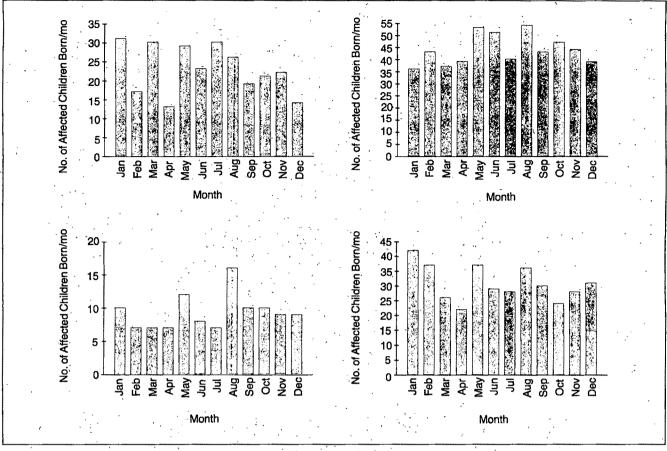


Fig 4.—Total number of affected infants born during each month with a major congenital neurologic malformation—top left, anencephaly; top right, spina bifida; bottom left, encephaloceles; and bottom right, hydrocephalus—during the period 1971 through 1987. No statistically significant seasonal differences were noted for any of the defects.

found significant variations in the Pacific region where hydrocephalus was more common and encephaloceles less common. However, as most duty assignments in the military last approximately 3 years, a sizable percentage of the study population may have been conceived in one geographic area and born in another. This factor could potentially reduce the differences between geographic areas.

Among a high proportion of infants with these four defects, we have found associated congenital malformations unrelated to the primary anomaly. Several of these malformations were found in infants with well-defined syndromes, such as the Meckel-Gruber syndrome (encephalocele, cleft palate, polydactyly, polycystic kidneys, ambiguous genitalia, and cardiac defects). Because unrelated anomalies occur so frequently with major CNS malformations, 1,27,41,42 all infants with these four CNS defects

should be examined closely during the neonatal period to detect any additional anomalies.

Neural tube defects are etiologically heterogeneous disorders, with at least seven major causative categories. We do not have enough specific information about our 1283 infants with CNS malformations to categorize their etiologic characteristics. Furthermore, we lack the information to enable us to predict the absolute percentage of anencephalic infants who could potentially serve as organ donors.

As with any retrospective analysis, our report should serve to generate hypotheses regarding the findings. We plan to monitor prospectively the features of major congenital CNS malformations in our population.

CONCLUSION

In a study population during a 17-year study period, we have found significant

declines in the incidences of major congenital neurologic malformations only among white females. We found black infants to be less likely to have spina bifida than white infants or infants of other races. Female infants overall are more likely to have neural tube defects than male infants, while the majority of hydrocephalic infants are male. We found no seasonal variations for these four defects, and the only geographic differences were found in the Pacific region for hydrocephalus and encephaloceles. Major neurologic malformations are common congenital abnormalities that are perplexing in their epidemiologic and demographic characteristics.

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Children of Mentally Retarded Parents

Pasquale J. Accardo, MD, Barbara Y. Whitman, PhD

E arly reports on the quality and duration of marriages that involve adults with mental retardation have documented both problems and possibilities.15 Today, adults with mental retardation are marrying and having children, and adult unmarried women with mental retardation (even moderate to severe mental retardation) are having children. The true prevalence of parents with severe intellectual limitation is unknown and possibly unknowable. An accurate differential diagnosis of the cause of cognitive deficiency in an adult who is living in the community is difficult to obtain in the absence of records of formal childhood testing. Nevertheless, in a key informer survey performed in the city of St Louis, Mo, the number of children of mentally retarded mothers, who were identified, suggested that adults with mental retardation were having children on the same order of magnitude as the rate in the general population, with a mean number of 2.8 children per retarded mother, who was identified, and a range of one to nine children per family.6 For a subset of such mothers who were directly tested, the IQ scores ranged from 35 to 69 (mean, 52); but, only 30% to 40% of the children who were tested scored in the mentally retarded range, and many of these results were clinically considered to be underestimates. In contrast to earlier reports,7 when the family size was compared with the maternal IQ, no trend toward an IQ-dependent differential fertility rate was observed.

ABUSE AND NEGLECT

Cognitive limitation in a parent has long been recognized as a risk factor for abuse and neglect in children. 8-11 In one

study, almost half (45%) of the children born to these mothers had been removed by the authorities. In a separate study, a retrospective review of comprehensive developmental assessments of 107 children from 79 families in which one or both parents were diagnosed as having mental retardation, child and family variables were investigated in an attempt to clarify risk factors in addition to parental cognitive limitation.12 These 79 families had 226 children (mean, 2.9; range, 1 to 9). The number of children in the home ranged from 0 to 6 (mean, 1.6) because 103 children had been removed or were no longer in the home (removal rate, 45.6%). Of the index children, 71 (66.4%) had suffered child abuse, sexual abuse, and/or child neglect. Of these 107 children, 31% were diagnosed as having mental retardation. Regardless of the presence of abuse or neglect, there was a tendency for the verbal IQ and receptive vocabulary scores to be lower than the performance IQ and full-scale IQ scores for all these children. Those children who were mentally retarded; who had lower IQ scores, who had lower verbal IQ scores, or who received a diagnosis of language disorder exhibited a lowered risk for abuse. (Receptive language scores, as measured by the Peabody Picture Vocabulary Test-revised, were not, however, strikingly different between abused and nonabused children.) In general, the children who were cognitively brighter and could talk better seemed more likely to be abused.

COGNITIVE DISSONANCE

The degree of parental cognitive limitation tended to be inversely related to the incidence of child abuse. However, when correlating a higher incidence of child abuse and neglect with a lower parental IQ, the following confounding effect must be allowed for: the ability to conceal successfully child abuse probably varies directly with the parental intelligence level. When parents are men-

tally retarded and experience the multiple other life stresses that are frequently associated with mental retardation, it is reasonable to anticipate that the family size will probably represent a major impact on these families' limited coping abilities. When the family size was cross-tabulated against the percentages of children who had been placed in foster care, who had been sexually abused, whose conditions had been diagnosed as failure to thrive, or who otherwise had been abused and neglected, clear trends were noted for an increased number of children in the family to parallel a rise in the incidence of these abusive situations, as well as for the percentage of children with none of these problems to decrease with an increasing family size. Finally, a review of individual case histories supported the clinical impression that the nature, extent, availability, and use of a personalsupport network (both extended families and community agencies) were major determining factors for the occurrence of identified abuse and neglect. The most interesting, if not completely unexpected, finding from this study was that abuse seemed more likely to occur with a decreasing parental IQ when this was combined with an increasing child IQ. The resulting cognitive dissonance or severe intellectual mismatch between parent and child appeared to contribute to the evolution of dysfunctional parent-child interactions.

PARENTING SKILLS TRAINING

Past attempts to minimize such abuse and neglect by teaching parenting skills to mentally retarded adults have tended to be either too broad or too narrow. ¹²⁻¹⁹ It is of concern that much of the optimism that derives from the success of intensive behavior modification research paradigms with such parents can be attributed to the inclusion of "mentally retarded" mothers with IQs near and often above 70. Our own clinical experience with a center-based pro-

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gram, Parents Learning Together, 20,21 yielded a much more mixed bag of successes and failures in which the IQ was not the sole or even the main predictor of a poor outcome. The retarded parents with whom we worked did not usually remember their children's birth dates. were not always able to recall the names of all their children or consistently distinguish one child from another (and sometimes even from themselves), and would often put the toddler's shoes on the wrong feet. In this population, one could never assume a routine of three meals per day, a normal wake-sleep/ day-night schedule, and safe, supervised structured play, much less the following of prescribed medication regimens.

The current literature on mentally retarded parents exhibits little sensitivity to the increased prevalence of a wide variety of other disabilities in this population. Complications, such as psychiatric disorders, hearing and vision impairments, learning disabilities, speech and language disorders, dental problems and physical handicaps, homelessness, poverty, large family size, and the absence of extended family support, all contribute to making retarded parents less able to benefit from such parenting skills training. Furthermore, the difficulties for these parents in meeting the developmental and behavioral needs of preschool children seem to intensify and become insurmountable with late school-age children and adolescents. On the one hand, a normal child of a retarded parent may be stressed to assume a "parental child" role. On the other hand, when such children exhibit, as they often do, various degrees of cognitive, language, emotional, and behavioral impairments, there is a decreased probability of their retarded parent either advocating for or effectively participating in any needed treatment intervention.

FUTURE DIRECTIONS

While each case needs to be decided on its own merits, the results of our own experience²² tend to confirm the pessimism of an earlier generation.⁴ The question with regard to parenting failure of significantly mentally retarded adults would seem to be not whether but when. Multiple-agency interventions often seem to add only to the preexisting chaos. The possibility that extended

family support, expanded-group home settings, foster home placements for the child/retarded parent dyad, or other alternative living arrangements might be formalized to respond adequately to the multiple needs of this population should certainly be explored.

A half century ago, the Iowa Study²² documented that severely deprived infants showed dramatic cognitive and behavioral improvements when they were placed in the care of "feebleminded" women. Instead of being interpreted as a demonstration of the beneficial effects of institutionalization, this poorly designed study has achieved near-mythic status in the behavioral science literature as proving the plasticity of infant intelligence in its ability to respond dramatically to minimal degrees of nurturance. But, in fact, neither this nor more recent studies even begin to address adequately the problem of parenting by significantly retarded adults. In a society that has not itself achieved much consensus about sexual behavior, marital stability, reproductive technology, abortion, and child care issues, a balanced approach to the questions that surround child rearing by mentally retarded parents can little hope to receive any reasoned response. Is childbearing by such persons an accident to be avoided at all costs, or is it an expected component of normalization? The current social service delivery system does not reflect any commitment on the part of society as a whole to envision childbearing by adults with significant mental retardation as a viable alternative. Intervention programs, such as our own, have demonstrated limited successes in the preschool years, but the problem does not appear to be remediable in the case of older children. The right of a child to a minimal expected level of parental competence would seem to restrict the child rearing, if not childbearing, rights of significantly retarded adults. Within the context of child abuse/neglect, the observed results of inadequate parenting must outweigh the mentally retarded parents' best intentions. There cannot be separate standards or expectations for adults of varying intelligence levels.24

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Three-Wheeled Vehicle Injuries in Children

Richard M. Ruddy, MD, Steven M. Selbst, MD

· Injuries associated with nonmotorized three-wheeled vehicles were prospectively evaluated through a standard questionnaire during the summer months at the emergency department of the Children's Hospital of Philadelphia, Pa. Fortyfour children, including 32 boys, with a mean age of 3.77 years, reported such injuries. Most fell (36.4%), but a second vehicle was often involved. Most children (33 of 44) were on low-slung Big Wheels. Head, neck, and dental injuries accounted for the majority. Most injuries were not serious. Two patients were admitted; both had fractures, one of them had a concussion. Data from the US Consumer Product Safety Commission corroborate the epidemiology of these injuries. Recommendations of safety precautions with nonmotorized three-wheeled vehicles are reviewed.

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Ricycle injuries in children have been recently reviewed by several sources1-8 as a cause of significant morbidity, but little attention has come to the toddler who is at risk while riding nonmotorized three-wheeled vehicles (3-WVs)-tricycles or "Big Wheels". Parents often ask questions regarding home and toy safety, and physicians may appropriately give advice to parents in the use of 3-WVs. A concern about these low-slung vehicles is the difficulty of seeing them from other vehicles (particularly cars) because 3-WVs are so near the ground. We surveved the presentation of all children at an urban emergency department (ED) associated with big wheel or tricycle injuries during a 6-month interval. Injury surveillance data from the US Consumer Product Safety Commission (USCPSC) on injuries associated with 3-WVs were reviewed to help estimate the scope of the problem and relate our patients to a larger population.

PATIENTS AND METHODS

All children with injuries associated with the use of 3-WVs, who were seen at the ED of the Children's Hospital of Philadelphia (Pa) from April 1, 1983, to October 1, 1983, were enrolled. The protocol was approved by the Committee for Protection of Human Subjects. At the ED triage station, a uniform injury questionnaire was attached to the charts for all victims of such trauma. Parents were asked by the attending physician to complete the questionnaire at the time of the visit. Demographic data were obtained. The questionnaire inquired about the circumstances of the injury, including time of day, when, where, and how the injury occurred. Questions were asked about the type of vehicle, how long the child had been riding the 3-WV, and whether it was known if the vehicle was broken or in need of repair. Inquiries were made concerning possible factors responsible for the injury as well as the patient's medical history. General questions regarding 3-WV use and safety precautions were asked. Forms were completed either at the time of the visits or within 48 hours. Data from the USCPSC's National Electronic Injury Surveillance System (NEISS) Network for tricycle injuries from 1982 to 1986 were reviewed in similar fashion. National estimates of injuries associated with 3-WVs were reviewed. Data on toy-related deaths gathered by the USCPSC from 1984 to 1987 were reviewed.

Questionnaire results were analyzed by frequency distributions. Factors that may have been associated with a greater number of serious injuries and admission to the hospital were analyzed by the χ^2 test. P < .05 was considered significant.

RESULTS

Forty-four children were treated at the ED of the Children's Hospital for 3-WV-related injuries. During this interval, there were 5207 trauma visits of

a total of 35 645 ED visits. The 3-WV injuries reported represent about 0.8% of trauma visits. Of the 44 children studied, 30 (68%) were 2 to 4 years old and 81% were less than 5 years old. Thirtytwo (73%) of the injured children were boys. Twenty (63%) of 32 injuries occurred in the evening from 4 to 8 PM. 9 (28%) occurred before 4 PM, and 3 (9%) occurred after 8 PM. Thirty-three (75%) of the injuries were related to the big wheel and 11 (25%) to tricycles. Reported locations where the injury occurred were as follows: sidewalk, 10 (22.7%); playground, 6 (13.6%); street. 4 (9.1%); and home, 5 (11.4%). There were 19 (43.2%) injuries where location was not reported. The ED of Children's Hospital primarily reflects inner city visits (approximately 80%) with suburban Philadelphia visits (approximately 20%). Of those known, most children were reported to have been injured while riding on the sidewalk. The injuries occurred less than two blocks from home in all 28 cases where the families informed the investigators. In 8 cases, there was a hazard on the riding "surface" reported by the parents (two holes, three bumps, two other hazards).

The tabulation below shows the reported mechanisms of injury, with the most common being falling off the vehicle.

How the Injury Occurred	No. (%)
Fell off the tricycle	16 (36.4)
Sidewalk problem	6 (13.8)
Lost control	5 (11.4)
Hit stationary object	4 (9.1)
Hit by moving car	3 (6.8)
Hit by bicycle (or big wheel)	3 (6.8)
Stunt-riding	3 (6.8)
Other	4 (9.1)

Seven injuries had involvement of a second vehicle (cars, 5; tricycles, 2), though the second vehicle was not always considered contributory to the injury by the parents. In 2 of 22 study patients, the 3-WV was reported as broken prior to the injury. The children had been

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				Location of Injury			Type of In	jury (%)			Hospital
Year	Total	<4 y Old (%)	M/F, %	Head/Face/Mouth (%)	Cancussion	Fracture	Laceration	Internal	Submersion	Auto	Admissions
1982	12794	9368 (73)	65/35	7684 (60)	105 (0.8)	701 (5.4)	6422 (50)	67 (0.5)	23 (0.17)	253 (1.8)	497 (3.8)
1983	11842	9070 (76)	64/36	7775 (66)	127 (1.0)	651 (5.4)	5794 (49)	150 (1.2)	22 (0.18)	364 (2.5)	306 (2.5)
1984	13350	9580 (72)	67/33	7867 (59)	148 (1.0)	1135 (8.5)	4891 (37)	115 (0.8)	114 (0.8)	316 (2.3)	428 (3.2)
1985	13 433	10382 (77)	66/34	8546 (64)	38 (0.2)	1029 (7.6)	6351 (47)	703 (5.2)		418 (3.1)	119 (0.8)
1986	14498	11 410 (78)	62/38	8590 (60)	285 (1.9)	1609 (11)	6297 (43)	683 (4.7)	102 (0.7)	81 (0.5)	405 (2.7)
Total	65 917	49810 (76)	65/35	40 462 (61)	703 (1.0)	5125 (7.7)	29755 (45)	1718 (2.6)	261 (0.3)	1432 (2.2)	1755 (2.6)

riding the 3-WVs for less than 1 month in 9 of the 20 cases reported, while 2 were riding the 3-WV for more than 1 year. The tricycle/big wheel was not thought to be the correct size for the child in 4 of 19 cases reported.

The following tabulation reviews the most common injuries. Head, neck, and dental injuries lead the list. Almost half the injuries were lacerations. There was only one child in this group who suffered "multiple" organ injuries (dental trauma and extremity contusion), which were not serious multiple traumas.

Body Part Involved Head and neck Lower extremity Dental Upper extremity Back and chest Abdomen	No. (%) 24 (54.5) 8 (18.2) 7 (15.9) 3 (6.8) 1 (2.3) 1 (2.3)
Type of Injury Laceration Contusion Abrasion Fracture	No. (%) 20 (47.8) 14 (31.8) 6 (13.6) 4 (9.1)

The majority of the children were treated and released from the ED (35/44, 79%). However, 2 (4.5%) were admitted and 7 others were referred to subspecialists. One of the admitted children was hit by a car while on a tricycle and the other was hit by a big wheel on the sidewalk. Both of these children had fractures (lower leg and skull). Both did well and were discharged in good condition in 24 to 48 hours.

Variables were compared by the type of injury (laceration vs fracture) and by severity of injury (minor—abrasions and contusions, vs moderate—lacerations and fractures). Age, sex, type of vehicle (big wheel or tricycle), previous medical history, road (surface) problem, and location of injury were not associated with significant differences by

	1984	1985	1986	1987
Submersion pool	3	1	2	6
Motor vehicle	3	2	7	5
Head trauma			2	
Collided with toy			1	
Fell off balcony				1
Fell				1
Hit lawn mower		1 -		
Total	6	4	12	13
All toy-re ated deaths	33	22	35	36

injury (type or severity). Referrals to subspecialists were more frequently made with a diagnosis of fracture. The number of fractures reported in the big wheel group (3 of 15) compared with that in the tricycle group (1 of 5) was not significantly different.

Data reviewed through NEISS from injuries reported during 5 years (1982 to 1986) to the USCPSC indicate that a significant number of 3-WV-associated injuries occur nationally.4 Estimate data from NEISS (based on computer estimates of reporting from approximately 80 hospitals nationwide) during the interval are summarized in Table 1. Most injuries involved the head and face in children less than 4 years old; most involved boys (almost 2:1compared with girls). Lacerations were reported most often (45%), but concussions (1.0%), fractures (7.7%), and internal injuries were also reported. There were an estimated 261 submersion injuries (0.3%). These were obviously serious, as most required hospitalization. At least 2.2% of estimated 3-WV injuries involved motor vehicle accidents, but this number may be underreported. At the NEISS reporting hospitals, 2.6% of injuries involving 3-WVs required admission (less than our 4.5% admission rate). Data from the NEISS do not distinguish between big wheels and tricycles.

The computer estimates of NEISS suggest a large number of 3-WV-associated injuries. A total of 10 000 to 15 000 ED visits associated with 3-WVs are estimated annually, and approximately 350 pediatric hospital admissions are estimated nationally. These encounters would produce medical charges exceeding several million dollars, and include children suffering from 1000 fractures, 100 concussions, and several hundred internal injuries.

Data on toy-related deaths reported by the USCPSC from 1984 to 1987 are listed in Table 2. From 1984 to 1987 are listed in Table 2. Injuries associated with 3-WVs accounted for 4 to 13 deaths in children per year during this interval. These mostly occured with either motor vehicle trauma or submersion injury in a pool or pond. Three-wheeled vehicles were associated with 30% of toy-related deaths reported to the USCPSC during this interval.

COMMENT

Injuries from nonmotorized 3-WVs have not been well described. Clearly there are fewer injuries requiring visits to the ED than with bicycle injuries (10 times more bicycle injuries presented at

the Children's Hospital ED during the same interval). In general, only an occasional patient with a 3-WV requires admission or suffers significant disability. Nevertheless, in view of the national estimates of 3-WV injuries and associated morbidity and mortality, the problem needs to be evaluated to consider possible prevention.⁴⁸

Injuries may occur after a fall when sudden turns of the front wheel cause the 3-WV to lose balance and tip over. This is supported by our data where many children fell off the tricycle (36.4%). Stunt-riding on the back of the 3-WVs and tipping over backwards only accounted for 6.8% of the presentations to our ED. This is much less common than the relationship of stunt-riding to bicycle injuries.1 Another concern is that many low-slung big-wheeled vehicles may not have tire treads on the wheels, which may increase the chance of accidents occurring from slipping. In addition, without brakes, children on big wheels would appear to be at additional risk from loss of control when going down graded paved areas.

Serious injuries associated with riding 3-WVs did occur on occasion. As our data suggest, one of the two admissions was related to being hit by a moving automobile. This is especially worrisome since 3-WVs are low on the ground and less visible than bicycles. Most low-slung big wheels are voluntarily sold with a "flag" which raises its vertical visibility. Use of these flags on 3-WVs was not screened for in data from us or NEISS. Since 3-WVs are mechanically simple vehicles, the number of injuries due to need of repair may not be important.

Three-wheeled vehicle-associated injuries do not seem to be as serious as bicycle-related injuries, but there are some similarities in risk factor. Bicycle

injuries have been reported to increase in rider faults near dusk, and our study revealed most 3-WV injuries also occurred from 4 to 8 PM. This may be from poor visibility, rider fatigue, or just the fact that this is the most frequent time to ride a tricycle. As with bicycle injuries, losing control of the tricycle (including falling off) is the leading problem associated with injury. Also, head. face, and dental trauma frequently are the injuries that most commonly bring children to medical care in both 3-WV and bicycle mishaps. Lower-limb trauma is a more common reason to be seen in the ED¹ for bicycle injury compared with our 3-WV injuries.

There were no reported deaths associated with tricycles or big wheels in the hospitals contributing to the NEISS estimates during this 5-year interval. However, deaths are reported through death certificates, voluntarily to the USCPSC, and this information was presented (Table 2). Contributing to the deaths in these cases were submersions/drownings and being struck by a motor vehicle. The overall low death rate may reflect the fact that toddlers rarely ride their 3-WVs in the street.

Recommendations to help decrease the frequency of injuries include action taken on the agent (3-WV), the environment (pavement, weather conditions, second vehicle), or the victim (rider). As for the agent, one design issue that may bear further evaluation is the "maximal allowable turning of the handlebars," which could contribute to "turning over." Reducing this handlebar-turning movement may decrease the maneuverability of the tricycle, but it may prevent the tricycle from turning too sharply. In addition, more tire tread may help prevent skidding. A report to the USCPSC on 23 in-depth investigations of low-slung tricycle injuries did not recommend any design changes. ¹⁰ The *environment* is difficult to alter, but parents should be sure that the riding surface appears free of hazards.

More importantly, young riders need adequate supervision and riding instructions to ensure safety. This is crucial to prevent riders from entering the street, other lanes of traffic, or water. It is not clear if children would benefit from the use of helmets on tricycles when they are likely to build up speed (eg, on a downhill run); however, it may be useful to begin the use of helmets in younger children to encourage the behavior as they grow older and ride bicycles or take greater risks. If Many of our recommendations are summarized as follows:

- 1. Supervise all young children.
- 2. Restrict the use of tricycles or Big Wheels to sidewalks, paths, and driveways (with careful supervision only).
- 3. Discourage riding down paths that lead to entering streets.
 - 4. Do not allow riding after dusk.
- 5. Equipment (ie, loose pedals, seats, wheels) checks should be done on a regular basis.
- 6. Do not permit stunt-riding or riding down steps.
- 7. Children with certain medical conditions may require restrictions or helmets for added safety. Helmets may protect children from sustaining head injury if they are likely to ride at higher speed.

We have modified the bicycle safety tips from the American Academy of Pediatrics' Committee on Accident and Poison Prevention. Further interventional studies may better define ways to reduce 3-WV-associated injuries.

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Evaluation of an Infant Car Seat Program in a Low-Income Community

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 This study was designed to assess the influence of an infant car seat loan program on car seat utilization in a lowincome community. An adjacent community, with no car seat program, was chocomparison. **Systematic** observations were made in the two neighborhoods, and this information was supplemented by telephone interviews. Greater use of infant seats was observed in the Intervention community (41%) than in the control community (27%) for infants younger than 6 months old. The rate of observed utilization of infants between 7 and 18 months of age increased to 50% on average, but no significant differences were noted between the two communities. These findings suggest that a communitybased loan program can produce shortterm increases in car seat use rates for infants, even in a low-income community. A strategy to facilitate continued accessibility to such restraints is needed, however, to maintain these improvements.

(AJDC. 1990;144:74-78)

It is now well known that child-restraint devices (CRDs) provide effective protection from the risks of injury and death associated with motor vehicle accidents and that hospital-based intervention programs are able to increase CRD use rates among middle-class families. However, few studies examine whether similar programs are efficacious among low-income groups, despite the fact that studies on the sociodemographic characteristics of re-

straint use consistently show an inverse association with socioeconomic status.⁵⁸

One program designed for low-income families has been described⁹ but was not rigorously evaluated. Another program designed to reach a broad range of socioeconomic levels illustrates the difficulty in reaching low socioeconomic status target groups. ¹⁰ To influence low-income target populations, community strategies may be needed. This approach is especially promising if community services with a preventive orientation already exist, as is the case for many neighborhood health centers.

This article examines the effectiveness of an infant car seat (ICS) loan program introduced in 1981 by a local community health center (LCHC) to increase the use of ICSs for children living in a low-income area of Montreal, Canada. The objective of the program was to increase the proportion of infant occupants of automobiles who were restrained by car seats. This evaluation examines the extent to which this was achieved and the extent to which the influence of the program was still measurable at the children's first birthday.

CAR SEAT LOAN PROGRAM

The program was established in a low-income neighborhood of downtown Montreal (St-Henri), with 22 000 inhabitants and approximately 250 births per year. The poverty rate was twice that of the surrounding region, 11 and 40% of the families with children were single parents. 12

The program was sponsored by an LCHC that provided, among a variety of other services, prenatal and postnatal information about the use of car seats, training in the use of these restraints, and ICSs on free loan. Pregnant women attending prenatal classes at the LCHC were given instruction about car seats in two 30-minute periods, one at the beginning and one at the end of each prenatal course. Parents were also shown a film on

child passenger safety, the correct use of car seats was discussed, and the loan program was advertised. Approximately 20% of pregnant women in the neighborhood enrolled in these prenatal courses. In addition, postnatal home visits were made to 95% of the newborns, during which a community health nurse provided 10 minutes of instruction about passenger safety. She then offered an ICS under the loan program for 9 months. When the ICS was returned, parents were encouraged to buy their own CRD, one suitable for older children, but no other incentives to do so were offered.

SUBJECTS AND METHODS

An adjacent community of similar socioeconomic status but with no ICS loan program was chosen for comparison. The study population comprised all children born from May 1981 to December 1982 in the target and comparison communities.

Because the target population for the program was all newborns in the community, and because outreach was a component of the intervention, the evaluation examined the influence of the program on the total community. It was not restricted to those parents who actually took advantage of the ICS loan.

Two methods of data collection were chosen because each has specific advantages—observations, which are generally more valid, and telephone interviews, which provide information about sociodemographic factors needed to adjust for differences between the areas being compared. Analyses were based on interviews, with data from observations used for validation.

Parents of children born during the first 18 months of the program were identified and interviewed by telephone, first when the child was 3 months old and then when he or she was 13 months of age. Eligibility criteria were as follows: single birth; ability of the mother to answer a questionnaire in French or English; and whether the child was a resident in the community at 3 months of age. Each interview asked about the possession and utilization of a CRD during the last journey, as well as questions about the mother's sociodemographic characteristics. The inter-

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viewers were fully trained to ensure consistency in the administration of the questionnaire and the coding of responses. They were part of a research team that was housed separately from those responsible for the execution of the educational and loaner program. Furthermore, they were not made aware of the main objectives of the program, and, hence, any potential for bias through, for example, leading questions or probes, was minimized.

Child-restraint device use was observed in the two communities on selected Thursday or Friday afternoons, and some Saturdays, during a 12-month period. These are times when a large number of children are traveling by car. Observers were placed at specified intersections and, for each vehicle carrying at least one child, they completed a checklist describing the way the child was transported and an estimation of the child's age (0 to 6 months or 7 to 17 months). The observers were also part of the research team and were "blinded" both to the hypothesis and the results of the interview. License numbers were recorded to establish the residence of the owner of the car to ensure that only residents of the study and control communities were counted in the observations. One hundred fifty-six infants aged 0 to 6 months and 487 infants aged 7 to 17 months were observed. A sample of 41 observations was made by two of the observers independently to establish interobserver reliability.3 The proportions of agreement were 93% for the restraint status of the child, 83% for the age group, 83% for seat belt use by the driver, and 100% for license plate numbers. The k values were .76, .54, .66, and 1.0, respectively. 13

Although the standardized observations provided consistent data on utilization, they were unable to determine whether the child was fastened by a harness, whether the seat was secured by a seat belt or for an infant older than 9 months, and whether the seat was anchored by a tether strap. The outcome measurements were, therefore, restricted to the possession and utilization of a CRD.

Statistical Analysis

The selected measurement of association between community of residence and program outcomes was the risk ratio (RR). The crude RR was estimated and its confidence interval was obtained by the method described in Kleinbaum et al¹⁴ in 1982.

The logistic-regression approach was used to measure the association between the community of residence (a proxy for the intervention), seat possession, and seat utilization, adjusting for the potential confounding effects of demographic differences between the two communities. The resulting adjusted odds ratio (OR) was transformed to an ad-

justed RR by the following relationship: RR = OR (1-P1)/(1-P2), where P1 and P2 are the rates of CRD in St-Henri and in the control community, respectively. The following possible confounding variables were controlled: marital status, education, parity, age of mother, and language. (The latter was included as an indicator of cultural values.) Interaction terms were added to the model to verify whether the effect of community of residence differed according to any of the covariates.

RESULTS

Of the 797 births in the two communities during the study period, 635 were eligible for the 3-month assessement (Fig 1). Ninety-eight percent of these parents were interviewed, and 88% stated they traveled with their children by car. These are the infants defined as at risk for passenger injuries, with regard to whom the short-term influence of the program was evaluated. From the cohort of infants eligible at 3 months, 80% continued to be eligible at 13 months. Ninety-eight percent of these parents were interviewed to assess the long-term effects of the program.

Characteristics of the Study Population

The sociodemographic characteristics of the eligible families who transport 3-month-old infants by car re-

vealed some possibly important differences between communities, as shown in Table 1. Mothers in St-Henri were younger, fewer had ever been to college, a larger proportion were single parents, and more were of French origin.

Short-term Utilization of ICSs

Sixty-one percent of the parents in the experimental community reported that they had an ICS for their 3-monthold child compared with 39.7% in the control community (unadjusted RR of 1.54). Two thirds of the St-Henri parents with a CRD had borrowed it from the LCHC. However, only 40.8% of all parents in St-Henri and 21.6% of those in the control community reported actually using the ICS on their last trip (Table 2). Observations made on infants younger than 6 months old confirmed the following reports: 40.7% vs 26.7% use in the experimental and the control communities, respectively. In both areas only a small proportion of the infants observed were in rearward-facing ICSs, and although the proportion was higher in the experimental community, the sample is too small to permit any solid conclusions.

Logistic-regression analysis found no significant interaction between intervention and the sociodemographic co-

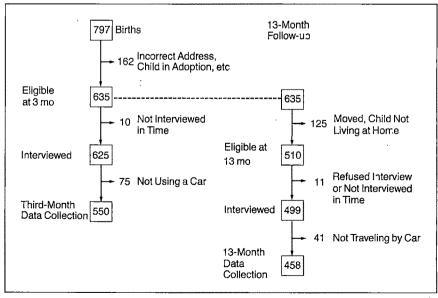


Fig 1.—Study population interviewed at 3 months and again 10 months later in the St-Henri and control communities.

Table 1.—Characteristics of Parents Who Transport Their Children by Car at 3 Months of Age

	Commu	nitles, %
Characteristics*	St-Henri (n = 336)	Control (n=214)
Age of mother, y		
(P<.001)		
15-19	15.0	3.7
20-24	37.9	37.4
25-29	31.8	34.6
30 or older	15.3	24.3
Education of mother		
(P<.001)		
Elementary	11.0	22.3
High school	74.7	40.8
College	14.3	36.9
Marital status		
(P<.05)		
Single parent	27.1	19.2
With spouse	72.9	80.8
Cultural origin		
(P<.001)		
French	86.0	51.9
English	11.6	7.9
Other	2.4	40.2
Parity		
Primiparous	48.8	55.8
Multiparous	51.2	44.2

^{*}Statistical analysis using χ^2 for marital status, parity, and cultural origin and t test for education and age of mother.

variates examined. Families in St-Henri had higher rates of possession and utilization of CRD than did those in the control community. The adjusted RRs were 1.48 for possession of a CRD and 1.90 for utilization of a CRD (Table 3).

As expected, the better-educated mothers had and used CRDs to a greater extent in both communities. However, even among mothers who did not reach high school, twice as many had a CRD in St-Henri (43%) than did those in the control community (21%), and more than twice as many (24% vs 9%) used it (Fig 2). If it is assumed that the loan program is responsible for these differences between the two communities, the effects of the program were not restricted to the better-educated parents.

Long-term Utilization of the ICS

To determine if the program had a long-term effect (ie, if, after having returned the borrowed seat at 9 months, parents in the experimental community bought a child car seat), telephone interviews were conducted at 13 months, and

observations were made at roughly the same time.

The rate of car seat utilization observed at this age increased in the two neighborhoods to 50%, but no significant differences were noted between the two communities. The rate reported on interview was 56%, and, again, no significant difference was seen between communities. Logistic regression, using the interview data, indicated that the adjusted results also showed no statistically significant differences (Table 3). It seems that this was because at 13 months of age, utilization of CRD in the control group improved to the level of the experimental group. Thus, we conclude that the superior performance in the intervention community when the child was 3 months old was not maintained by age 13 months.

COMMENT

The main result indicates that an ICS loan program implemented in a low-income community increases utilization of CRDs by parents of children younger than 6 months. However, once the child had grown out of the ICS, the difference between the two communities did not persist because of improved restraint rates in the control community.

The finding that restraint use was increased among children older than 6 months seems to contradict other studies. ¹⁵ It could be that restraint use increased among older children as a historical effect, but because most other studies group infants younger than 1 year into a single category, this may obscure a genuine increase in use during

	,		%	******			
		Observations			Interviews		
Infant Car	St-Henri	Control	Difference	St-Henri		Difference	
Seat Outcomes	(n = 81)	(n = 75)	(95% CI)	(n=336)		(95% CI)	
Possession	Not available	Not available	Not available	61.0	39.7	21.3 (10.6, 27.5	
Utilization	40.7	26.7	14.0 (0.7, 28.7)	40.8	21.6	18.2 (11.5, 26.7	

^{*}Unadjusted results. Cl indicates confidence interval.

	Table 3.	-Possession and Utiliz	ation of CRDs*	
			%	
Ob and do some of		Crude	•	Adjusted†
Short-term and Long-term Outcomes	St-Henri	Control	RR (95% CI)‡	RR (95% CI)
At age 3 mo	(n = 336)	(n = 214)	• • •	• • •
Possession of CRD	61.0	39.7	1.54 (1.28 to 1.85)	1.48 (0.97 to 2.26)
Utilization of CRD	40.8	21.6	1.89 (1.42 to 2.52)	1.90 (1.19 to 3.02)
At age 13 mo	(n = 276)	(n = 182)	• • •	• • •
Possession of CRD	65.1	66.3	0.98 (0.86 to 1.13)	0.90 (0.54 to 1.52)
Utilization of CRD	56.4	54.3	1.04 (0.88 to 1.23)	0.92 (0.57 to 1.50)

^{*}CRDs indicates child-restraint devices. Results obtained at ages 3 and 13 months. Crude and adjusted results are from the interview survey.

[†]By means of a logistic regression.

[‡]RR indicates risk ratio; OR, odds ratio; and CI, confidence interval. RR = OR (1 - P1)/(1 - P2), where P1 and P2 indicate the rates of CRD in St-Henri and in the control community, respectively.

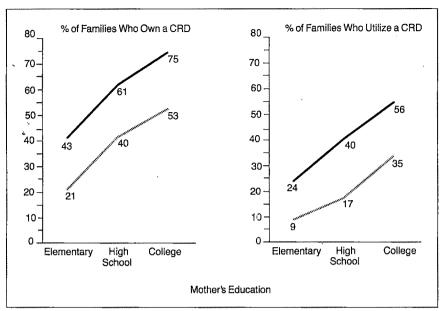


Fig 2. —Possession and utilization of child-restraint devices (CRDs) at age 3 months according to level of education. The results are unadjusted. Solid lines indicate St Henri community, and diagonal lines, control community.

the last half of the first year. In a larger observational study done in Montreal, the use of ICSs was found to be lower in infants younger than 6 months (41%) than at age 7 to 18 months (53%), and use rates increased with socioeconomic level. Thus, it seems that the experimental program stimulated parents to use carriers earlier than they would have done otherwise. There is, however, no evidence that the program modified the behavior of parents in the long-term. Future programs must find ways to facilitate access to restraints when the child grows out of the ICS.

Similar observed and reported rates are surprising in light of the results reported elsewhere. However, it is reasonable to assume that observed rates are accurate. It may be that the previously reported differences were obtained when use rates were generally lower than those found in this survey. Furthermore, this agreement may be because low-income respondents are less concerned with the social desirability responses of their reports, ie, less inclined to exaggerate.

This evaluation did not attempt to identify the specific elements of the program that made it effective—the loan, which was intended to increase accessibility, or the education, which was intended to increase motivation. The importance of the loan is obvious,

however, as indicated by the higher proportion of parents in St-Henri who had an ICS when their child was 3 months old. The educational part of the program also seems to have been useful because a larger proportion of parents of St-Henri with ICSs actually used them.

One drawback of this evaluation design is that the rates of use before the intervention are unknown. We assume that any differences between the two communities before the program would be explained by the demographic characteristics that were controlled in the regression analysis. Although other community seat belt interventions aimed at parents were introduced during this period, none were directed exclusively at the experimental community, and we, therefore, concluded that the program was responsible for the superior rates of utilization for children younger than 6 months.

One strength of this study was its community-based orientation and its attempt to measure the effect of the program on the total population for which it was intended, rather than only on those who benefited directly from the service. Possession and utilization of a CRD at age 3 months by children of less-educated mothers indicated the success of the program in families usually less likely to participate in preventive actions.

Can these results be generalized to

other populations, and, specifically, to those in the United States? It seems that the most important factor influencing the generalizability of results is the presence of a seat restraint law applicable to this age group and the nature of the enforcement and sanctions associated with such laws. When this study was conducted, Quebec had a seat restraint law that applied to front-seat occupants but excluded those in the rear seats. More than 90% of observed infants were in the back seat. Currently, throughout the United States and Canada, restraint laws applicable to children are in effect, and although enforcement and sanctions no doubt vary greatly, it seems likely that because of this fact any similar program would be even more successful.

These results clearly suggest that the goal of any program of the kind described must not be limited to simply getting parents to install safety seats, but must include measures to ensure their proper and consistent use. The addition of air bags, either through voluntary or regulatory processess, is only part of the solution to this problem and may, in fact, be inadequate for infants, since there is, as yet, little evidence demonstrating that they are as effective for infants as they seem to be for adults. They may actually prove to be detrimental if they are incompatible with automatic belts or stimulate complacency about the use of well-designed infant carriers.

The community approach seems to offer a valuable alternative to hospitalbased rental services because it can consider the families' values and cultural factors through individualized contacts during home visits. In particular, a program for low socioeconomic groups is more likely to succeed if it is based on the language and values of that community. Also, when the target population lives in the same area, local newspapers and posters may be used to reinforce the message. This may help to include restraint use into the repertoire of culturally accepted preventive health behaviors. 17 In the spirit of health for all by the year 2000, more interventions should be developed that focus on populations at greatest risk, ie, those least likely to adopt effective means of prevention without such guidance.

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Book Review

Immunologic Disorders in Infants and Children, 3rd ed, edited by E. Richard Stiehm, 843 pp, \$230, Philadelphia, Pa, WB Saunders Co, 1989.

A working knowledge of immunology is as important to pediatricians as is a working knowledge of biochemistry, genetics, pharmacology, or any of the other "basic sciences." For example, the primary immunodeficiency diseases are not nearly as uncommon as originally supposed; a new secondary immunodeficiency disease, acquired immunodeficiency syndrome, has touched nearly every practice. There is a growing appreciation that the immune system is important in the pathophysiology of a variety of pediatric illnesses. The third edition of this classic text successfully combines both basic and clinical immunology into one book and is the one immunology text pediatricians should have on their shelf.

The book is divided into three sections. The first section covers basic immunology, with special attention paid to developmental aspects; the second section focuses on immunodeficiency diseases, both primary and secondary; and the third section is a review of immunologic aspects of pediatric illnesses. The first section on basic immunology is written with the clinician in mind and is a valuable resource to anyone who wishes to learn the basic principles of immunology. The chapters on the ontogeny of immunity and the mucosal immune system are especially well done. The second section on immunodeficiency diseases is the most comprehensive and authoritative of its kind. The chapters on the immunodeficiency of immaturity and the general considerations of the immunodeficiency diseases are especially relevant to pediatricians and are difficult to find in other texts. Finally, the third section on immunologic aspects of pediatric illnesses details the immunologic basis for the underlying pathophysiology of hundreds of pediatric disorders and will be of use to pediatricians in a wide variety of disciplines other than immunology.

Although multiauthored texts have become the norm, they are often uneven in style and content, which makes it difficult for the reader to appreciate the field, or book, as a whole. Stiehm has accomplished a difficult task by making each chapter relate to the others with respect to both emphasis and content, and to some degree, style. The chapters were written by highly knowledgeable contributors who have first-hand experience with their subject matter, whether in the laboratory or at the bedside, and who can also communicate effectively. The book is encyclopedic but highly readable. The references at the end of each chapter are extensive, often numbering into the hundreds, making the book especially valuable to those readers who wish to go to the original literature.

This edition contains updated sections on new diagnostic tools, new diseases, such as the acquired immunodeficiency syndrome, and new therapeutic modalities, such as intravenous immunoglobulin therapy and haploidentical bone marrow transplantation. Unfortunately, the book does not have a separate chapter on pediatric acquired immunodeficiency syndrome, making it somewhat difficult to find information on this important disease. However, the index is quite good and the information on the acquired immunodeficiency syndrome can be found even though it is scattered among the various chapters.

This is an excellent book! If you are going to have only one book on immunology—basic, clinical, or both—this is the one to have.

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Childhood Injury Mortality in Ohio, 1979 to 1986

Setting Priorities for Prevention

Richard S. Hopkins, MD, MSPH; James V. Writer, MPH; B. Kim Mortensen, PhD, MPH; Robert W. Indian, MS

 Injury deaths in Ohio children aged 1 to 16 years account for less than 0.5% of all deaths in the state but 6% of all years of life lost before age 65 years. In this study, injury mortality rates were calculated by sex for three age groups (1 to 5, 6 to 11, and 12 to 16 years) and three population groups (metropolitan white, metropolitan nonwhite, and nonmetropolitan). The 15 metropolitan counties were those with a central city of at least a population of 50 000, containing 60% of the state's population. Fire is the leading cause of injury mortality for metropolitan children aged 1 to 5 years, while motor vehicle injuries and drowning are the leading causes for nonmetropolitan children in this age group. Fire is also the leading cause for metropolitan nonwhite children aged 6 to 11 years, while motor vehicle injuries are the leading cause for nonmetropolitan children, and pedestrian injuries are the leading

I njury deaths in Ohio children aged 1 to 16 years account for less than 0.5% of all deaths in the state but 6% of all years of life lost before age 65 years. To identify high-risk populations in children aged 1 to 16 years, mortality rates were calculated for the seven leading causes of traumatic death for the years 1979 through 1986 by race, sex, and type of community. This analysis focuses on the serious injuries that have led to death and presents calculations of excess deaths by age, injury type, and population group to help identify priorities for prevention efforts. Information

cause for metropolitan white children. For nonmetropolitan and metropolitan white children aged 12 to 16 years, motor vehicle injuries are the leading cause, while for metropolitan nonwhite children homicide is the leading cause. Excess deaths for each cause were estimated by calculating the number of deaths expected for each age group if the rate experienced by the second-lowest population race group had applied to the whole population in that age group, and comparing this with the observed number. Using this approach, highest priority would be placed on prevention of motor vehicle deaths in 12- to 16-year-old nonmetropolitan and metropolitan white children, of fire deaths in metropolitan nonwhite children aged 1 to 11 years, and of drowning deaths in boys aged 12 to 16 years in all three population groups.

(AJDC. 1990;144:79-82)

on the occurrence of serious nonfatal injuries and of the common less serious injuries of childhood would also be helpful in setting priorities but is not available on a statewide basis in Ohio.

METHODS

An injury death was included in the study if it occurred to an Ohio resident 1 to 16 years of age. Injury deaths were those falling in the range E800-E999 in the International Classification of Diseases, Ninth Revision. 1 The two types of communities studied are referred to as metropolitan (the 15 Ohio counties containing a city of greater than 50 000 persons in 1980) or nonmetropolitan (the remaining 73 Ohio counties). As nonwhite children account for fewer than 4% of nonmetropolitan children, all nonmetropolitan children were considered as a group irrespective of race. Metropolitan children were classified as either white or nonwhite. In Ohio, approximately 95% of nonwhite children statewide are black; the remainder are members of a great many diverse groups. Children were divided into three age groups: preschool, aged 1 to 5 years; elementary

school, aged 6 to 11 years; and secondary school, aged 12 to 16 years. There were 1 305 326 nonmetropolitan children aged 1 to 16 in Ohio in 1980, 1 628 554 metropolitan white children, and 400 362 metropolitan nonwhite children.²

We estimated excess deaths for each cause by calculating the number of deaths that would have occurred if the observed rate for the second-lowest race-sex-community group within each age group had applied to all children of that age. We divided the difference between this number and the observed number of deaths by the observed number to arrive at a percentage that were in excess. We used the rate for the second-lowest race-sex-community group as a conservative estimate; we reasoned that the lowest rate might be a statistical outlier.

RESULTS

From 1979 through 1986, 7938 children from 1 to 16 years of age died in Ohio from all causes, 4212 (53.1%) as a result of injuries. Mortality rates from all injuries are highest for metropolitan nonwhite children, and lowest in metropolitan white children (Fig 1). The number of deaths in boys exceeded the number in girls in each category.

The seven leading categories of injury account for 79% of injury deaths in these children. Motor vehicle occupant injuries are the leading injury cause of death for all children in Ohio (1030 deaths, 4.73 per 100 000 per year). Fire is the leading cause among metropolitan nonwhite boys and girls and among metropolitan white girls. Motor vehicle occupant injuries are the leading cause of death among the other three sex-racegeographic groups; the highest rate is in nonmetropolitan boys, at 8.1 per 100 000 per year. The annual rates of fire and homicide deaths in metropolitan nonwhite boys are also very high, at 7.4 and 7.3 per 100 000, respectively.

The ranking of injury death rates by

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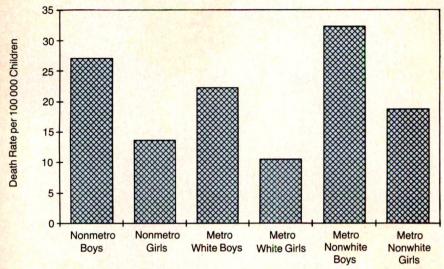


Fig 1.—Average annual death rate from injuries of all causes, by sex and population group, in Ohio children aged 1 to 16 years, 1979 to 1986. Nonmetro indicates nonmetropolitan; metro, metropolitan.

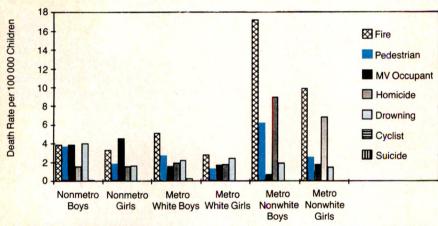
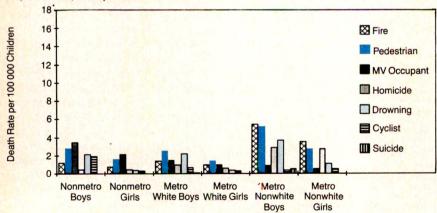


Fig 2.—Average annual death rates by cause of injury, sex, and population group in Ohio children aged 1 to 5 years, 1979 to 1986. MV indicates motor vehicle; nonmetro, nonmetropolitan; and metro, metropolitan.

Fig 3.—Average annual death rates by cause of injury, sex, and population group in Ohio children aged 6 to 11 years, 1979 to 1986. MV indicates motor vehicle; nonmetro, nonmetropolitan; and metro, metropolitan.



cause varies by age group (Figs 2 to 4), thus the leading cause for preschool children, aged 1 to 5 years, is fire; for elementary-school children, aged 6 to 11 years, it is being struck by a vehicle while on foot (pedestrian deaths); and for secondary-school children, aged 12 to 16 years, it is motor vehicle crashes.

For children aged 1 to 5 years (Fig 2), fire is the leading cause of injury death in the four metropolitan groups; for nonmetropolitan children, drowning is the leading cause in boys and motor vehicle occupant injuries are the leading cause in girls, followed closely by fire in both sexes. Death rates from fire in metropolitan nonwhites are far higher than from any other type of injury and largely account for the excess death rate from injury in this group compared with the other two geographic groups. These children also have over three times as high a death rate from homicide as the metropolitan white or nonmetropolitan children.

For children aged 6 to 11 years (Fig 3), while pedestrian fatalities are the leading cause statewide, nonmetropolitan children have higher rates for motor vehicle occupant deaths than for any other cause; for metropolitan nonwhite children, fire remains the leading cause. For both these groups, pedestrian fatalities are in second place.

For children aged 12 to 16 years, injuries to motor vehicle occupants account for over one third of injury deaths and are the leading cause statewide (Fig 4). Rates for nonmetropolitan boys, at 16.9 deaths per 100 000 population per year, are somewhat higher than in metropolitan white boys (11.5 per 100 000) and over five times as high as in metropolitan nonwhite boys (3.0 per 100 000). A similar pattern is seen for girls, with slightly lower rates. For metropolitan nonwhite children in this age group, homicide is the leading injury cause of death by a wide margin, at 10.8 per 100 000 in boys and 5.2 per 100 000 in girls. These rates are four to six times as high as those in metropolitan whites or in children from nonmetropolitan areas.

For the seven leading causes of injury death, the average annual number of deaths observed was 416 (Table). If the rates observed for each cause in the second-lowest race-sex-community group in each age category had applied to all

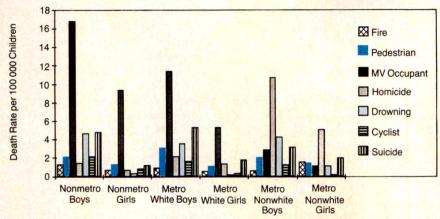


Fig 4. - Average annual death rates by cause of injury, sex, and population group in Ohio children aged 12 to 16 years, 1979 to 1986. MV indicates motor vehicle; nonmetro, nonmetropolitan; and metro, metropolitan.

Age Group	MV	Cyclist	Pedestrian	Drowning	Fire	Suicide	Homicide	Total
1-5 y		250000						
Rate in second- lowest group	1.59	0.07	1.92	1.67	3.34	0.0	1.82	
Expected deaths	12.3	0.5	14.8	12.9	25.1	0.0	14.1	
Observed deaths	20.5	1.1	20.9	19.2	39.6	0.0	19.7	
Excess deaths	7.2	0.6	6.1	6.3	14.5	0.0	5.6	
6-11 y				No. of Contract of				
Rate in second- lowest group	0.97	0.38	1.71	0.44	1.05	0.0	0.51	
Expected deaths	9.9	3.9	17.5	4.5	10.7	0.0	5.2	
Observed deaths	18.9	8.2	24.8	15.2	16.0	0.7	9.9	
Excess deaths	9.0	4.3	7.3	10.7	5.3	0.7	4.7	
12-16 y								
Rate in second- lowest group	3.0	0.39	1.35	0.43	0.69	1.84	1.45	
Expected deaths	27.8	3.6	12.5	4.0	6.4	17.1	13.4	
Observed deaths	89.4	11.5	17.9	21.5	8.7	30.9	21.4	
Excess deaths	61.6	7.9	5.4	13.5	2.5	13.8	8.0	
All ages					MA			
Expected deaths	50.0	8.0	44.8	21.4	42.2	17.1	32.7	216.
Observed deaths	128.7	20.9	63.5	56.0	64.4	31.6	50.9	416.0
Excess deaths	78.7	12.9	18.7	34.6	22.2	14.5	18.2	199.8
Percent excess	61.1	61.7	29.4	61.8	34.5	45.9	35.8	48

^{*}The death rate was per 100 000 children, 1980 census as denominator. MV indicates motor vehicle occupant.

children in that age category, the number of injury deaths would have totaled 216.2, a reduction of 48.0%. This excess fraction of deaths ranged from 29.4% for pedestrian deaths to 61.8% for drowning deaths. The largest number of excess deaths was for motor vehicle occupant injuries, with an estimate of almost 79 excess deaths per year.

COMMENT

Injuries resulting from motor vehicle crashes are the leading type of fatal injury in Ohio children in spite of a child passenger restraint law implemented partway through the period. Fire and homicide are the leading causes of injury death among metropolitan nonwhites. For several injury types, metropolitan children, unlike metropolitan residents.3 have higher mortality rates than nonmetropolitan children.

Injury is a frequent event while growing up,46 but the variation in mortality rates indicates that many fatal injuries are preventable. The analysis of excess injury deaths gives some guidance for the most profitable direction for injury prevention efforts and further research, although these estimates contain a wide margin of uncertainty. The assumption underlying these calculations is that low injury death rates, comparable with those seen in the lowestrisk race, sex, and geographic groups, can be achieved in the whole population. Achieving these lowest observed rates should be seen as a long-term goal, because there may be social, institutional, and economic barriers inhibiting widespread application of effective injury prevention measures. The population groups studied also vary greatly in their exposure to injury hazards, such as motor vehicles, bicycles, and swimming pools. On the other hand, it may eventually be possible to reduce injury death rates below those observed in low-risk populations today.

In some cases injury prevention efforts will consist of applications of preventive measures of known effectiveness, while in other cases they will consist of research to identify and/or evaluate new strategies. Any one of the following three criteria could be used in deciding which causes to give a high priority for such efforts: (1) the absolute number of deaths due to each cause, (2) the fraction of deaths from each cause that are in excess, or (3) the number of excess deaths from each cause.

Using the first criterion, in the state as a whole emphasis would be placed on preventing motor vehicle occupant, pedestrian, and fire injuries. Using the second criterion, emphasis would be placed on reducing motor vehicle occupant injuries, drownings, and injuries to cyclists. Using the third criterion, emphasis would also be placed on preventing motor vehicle occupant injuries and drownings. All three of these criteria give considerable weight to the causes of death where high rates affect large populations. The second and third criteria also give weight to causes of injury death that are high in some groups but low in others, so that the potential for prevention appears to be greatest. Using the second or third criteria results in giving relatively less importance to pedestrian and fire injuries.

While this method has been applied here to Ohio mortality data stratified by age, sex, geographic area, and race. a similar analysis could be applied to other geographic areas whose populations experience varying incidence, hospitalization, or mortality rates for specific causes of injury. While it will not always be true that the low rates observed in some groups of the population can in principle be achieved in the whole population, the difference between the number of events observed and the number expected if the lower rate had applied to the whole population may define a reasonable goal for prevention programs to attempt to achieve.

In Ohio, this modestly detailed analysis of childhood injury mortality data has also allowed us to identify certain population groups who are experiencing

unacceptably high mortality. These are also generally the groups that contribute the largest number of excess deaths in the analysis (Table): (1) nonmetropolitan and metropolitan white children aged 12 to 16 years, for whom motor vehicle occupant deaths are by far the leading cause of death; (2) metropolitan nonwhite children aged 1 to 5 and 6 to 11 years, who die of injuries from fire and flames at a rate approximately four times that of other children their age; (3) boys aged 6 to 11 and 12 to 16 years in all groups, who experience a marked excess of drowning deaths compared with girls their own age in their own geographic and race groups; (4) boys aged 12 to 16 years, whose suicide mortality rates substantially exceed those of girls in all population groups; (5) metropolitan nonwhite boys and girls aged 12 to 16 years, who have by far the highest rate of homicide death (10 per 100 000 per year in boys and 5 per 100 000 per year in girls); (6) nonmetropolitan boys aged 6 to 11 and 12 to 16 years, who sustain a rate of bicycle injury deaths three to five times as high as that of

other groups their age; (7) metropolitan nonwhite boys aged 1 to 5 and 6 to 11 years, who have the highest rates of pedestrian fatalities; and (8) metropolitan nonwhite children aged 1 to 5 years, who also die as a result of homicide at a rate approximately four times that of other children.

Prevention efforts applied to these groups would be expected to have the largest impact on childhood injury mortality in Ohio. A similar analysis carried out in another state or geographic area could be expected to have broadly similar results, but may differ because of differing population characteristics, differences in the prevalence of injury hazards, or differences in the effectiveness of injury control efforts already in effect.8 Information about the circumstances leading to injury in various age, sex, ethnic, and geographic groups would be needed to design and target prevention efforts effectively, as would information about the costs and effectiveness of specific interventions.

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Attitudes Toward Bicycle Helmet Ownership and Use by School-age Children

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• To identify attitudes toward bicycle helmet ownership and use, questionnaires were sent to parents of 2178 thirdgraders; 1057 (48.5%) returned valid responses. Of 931 children who had bicycles, 24% owned helmets, but only 56% of children who owned helmets wore them. Helmet ownership, but not use, was associated with higher parental education. Fifty-one percent of 704 parents of bicycle owners who had not purchased helmets said they had never thought of it, 29% thought helmets were too costly, and 20% felt their children would not wear them. Of 792 children who did not wear helmets, 25% said they did not wear them because their friends did not; 22% never thought about wearing helmets; and 16% found them uncomfortable. Efforts to increase the wearing of helmets should address helmet design, awareness, peer pressure, and cost.

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Bicycling injuries to children and adolescents accounted for over 400 000 emergency department visits and 500 to 600 deaths in the United States in 1986. Studies²⁷ have shown that most bicyclerelated hospital admissions and deaths have been due to injuries to the skull and brain. More than 20% of all significant brain injuries in those aged 14 years or less may be bicycle related⁶; these injuries can result in severe long-term disability as well as death. ^{6,7}

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Use of bicycle helmets may be one way to reduce the incidence of head injuries among children. ^{8,9} Currently, bicycle helmets are subjected to physiomechanical testing ¹⁰ similar to that used for motorcycle and football helmets, which have been shown to significantly decrease the frequency of head injuries. ¹¹⁻¹³ A recent case-control study ¹⁴ of injuries resulting from bicycle crashes found that bicycle helmets reduced the risk of head injury in bicycle crashes by 85%. This suggests that helmets are an effective intervention for the prevention of bicycle-related head trauma.

Few children presently wear bicycle helmets. In 1985 Weiss¹⁵ observed white middle-class children and young adults commuting to and from school by bicycle in Tucson, Ariz. He found that the prevalence of helmet use was less than 2% in school-age children, compared with 10% in college-age riders. Wasserman et al¹⁶ interviewed bicyclists at roadside, and found that only 4% of those who were 10 to 21 years old were wearing helmets.

Commonly suggested reasons for the failure of many children to wear bicycle helmets include high cost, uncomfortable design, peer pressure against wearing them, and lack of perceived need. 7.8,16 A survey of physicians who treat children revealed that the majority believed lack of parental awareness to be the reason so few children wear helmets. 17 There are, however, no published data on parental attitudes toward buying bicycle helmets for their children, or on the attitudes of young children toward wearing them.

The primary purpose of this study was to determine what attitudes were held by parents and their school-age children toward owning and wearing bicycle helmets. We also wished to determine the reported prevalence of helmet ownership among these children in Se-

attle and to estimate use among helmet

METHODS

Questionnaires were mailed to the parents of 2178 children randomly selected from all 3231 third-graders registered in Seattle public schools for the 1986-1987 school year. Third-grade children were chosen because they were the focus of a community-based campaign to increase helmet use. The survey was sent to one half of the sample in June 1987 and to the other half in October 1987: sample size was calculated to enable evaluation of potential changes in attitude resulting from campaign activities by comparing the second sample with the first. However, the campaign ultimately mounted only limited activities during 1987 and did not peak in intensity until 1988, so all results reported here were essentially "precampaign." Direct observations of helmet use conducted simultaneously found no change in use between May 1987 and September 1987. 18 Except as noted below, results of the two surveys were similar and have been combined.

Reminder postcards were sent 2 weeks after the initial mailing, and second questionnaires were sent to nonresponders 2 weeks later. Parents were asked about bicycle and helmet ownership, any reasons for not buying a helmet, attitudes toward helmet effectiveness and the likelihood of bicycle-related injuries, other health- and safety-related behaviors, and demographic data. Parents were requested to give the last page of the questionnaire to the child to complete. The children were asked whether they wore a helmet the last time they rode their bicycle, and if not, why not.

Aggregated data were available from the Seattle public schools on the total third-grade population for age, sex, and whether they were living with a parent, guardian, or other person. Addresses (with zip codes) were available for all of those sampled, including those who did not return the questionnaire (nonresponders). The socioeconomic status of responders vs nonresponders was compared using 1980 census data on zip code median income and proportions of high

school graduates living in each zip code.

 χ^2 tests and t tests were used to test for the statistical significance of relationships between study variables. Logistic regression was used to determine the association of helmet ownership and use with multiple variables simultaneously.

This study was approved by the Institutional Review Board of the University of Washington.

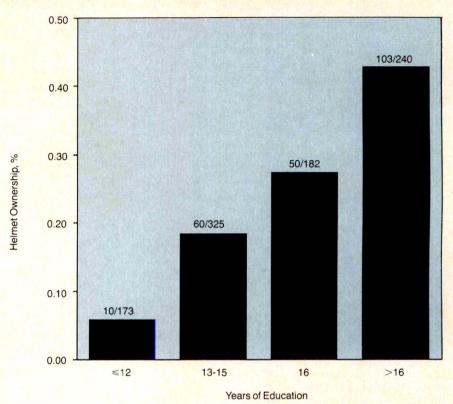
RESULTS

Of the 2178 questionnaires sent, 24 were returned as undeliverable, 6 were returned from addresses outside the Seattle Public School District, and 8 yielded unusable responses. There were 1057 valid responses, giving a response rate of 48.5%.

The mean (SD) age of the third-grade child in respondent households was 9.1 (0.6) years; there were 517 boys (49.1%) and 535 girls (50.9%). These values were similar to those for the third-grade population as a whole, whose mean age was 9.1 on September 1, 1987, with 51.3% boys and 48.7% girls. Almost all (95.4%) of the questionnaires were completed by parents rather than legal guardians or other persons; in the third-grade school population, 96% of children lived with one or both parents.

The sampled families were grouped into approximate quartiles according to the proportion of high school graduates living in the same zip code, as a proxy for socioeconomic status. Comparisons between responders and nonresponders based on this zip code information revealed that those parents who lived in zip codes with high proportions of high school graduates were significantly more likely to respond to the questionnaire than were parents living in zip codes with lower proportions of graduates; according to proportions of high school graduates, the response rates in descending order for the quartiles were 56%, 56%, 44%, and 39% (χ^2 trend test, P < .001). Respondents living in zip codes with higher proportions of high school graduates were also more likely to report having purchased helmets for their children, with reported ownership rates of 38%, 21%, 15%, and 18% for the same quartiles (P < .001).

There were also statistically significant differences in median income of zip code between responders and nonresponders, but there were no important



Percent helmet ownership by parental level of education.

differences in zip code median income between helmet owners and nonowners (data not shown).

Helmet Ownership and Covariates

Nine hundred thirty-one children (88.1%) in respondent households owned bicycles, of whom 223 (24%) reported owning helmets. The gender distribution of owners and nonowners was similar. Parental level of education as reported by respondents strongly correlated with bicycle helmet ownership, as shown in the Figure. Fewer than 10% of parents with a high school degree or less reported ownership, compared with more than 40% of those with education beyond college.

Bicycle helmet ownership was positively associated with health- and safety-related attitudes and knowledge, even after controlling for parental education and other covariates in the multivariate model. The odds of helmet ownership were 7.6 times higher (95% confidence interval [CI]: 1.8, 32.6) for parents who wore seat belts usually or always than for other parents. Helmet ownership was more likely if the respondents believed in the likelihood of an

injury resulting from a crash (odds ratio [OR] = 2.0; 95% CI: 1.6, 2.5) or if they believed that helmets were likely to prevent head injuries in such crashes (OR = 1.6; 95% CI: 1.2, 2.0). A bicycle injury occurring in the preceding year to a child in the respondent household was positively associated with helmet ownership (OR = 3.1; 95% CI: 1.1, 8.4), as was knowledge of a serious bicycling injury to anyone known to the respondent (OR = 1.9; 95% CI: 1.3, 2.8).

Reasons for Nonownership

The reasons given by parents for not purchasing helmets for their children are shown in Table 1. By far the most common reason was that they had never thought about purchasing a helmet (n=359,51%). There was a statistically significant change in this proportion between June, when 57% of parents indicated this reason as important, and October, when 46% did (P<.01). It remained, however, the most frequently given reason for each time period. All other reasons had similar frequencies in the two time periods.

Parents who chose the reason "never

Table 1.—Prevalence of Parents' Reasons for Not Purchasing Bicycle Helmets

Reasons	No. (%) of Parents (n = 704)
Never thought about purchasing	359 (51)
Helmet costs too much	206 (29)
Child would not wear helmet	144 (20)
Helmet not needed*	88 (12)
Procrastination	47 (7)

^{*}Reasons given included child seldom rides, only rides "around the neighborhood," or only rides where it is safe.

thought about purchasing" were less likely to be college graduates than were those who did not choose this reason (29% vs 48% college graduates; OR = 0.4; 95% CI: 0.3, 0.6). In contrast, parents who chose the reason "child would not wear helmet" were more likely to be college graduates (47% vs 36% college graduates; OR = 1.5; 95% CI: 1.0, 2.3), as were those who chose the reason "helmet not needed" (57% vs 36% college graduates; OR = 2.4; 95% CI: 1.5, 3.8). There was little difference in education among those parents who did or did not choose "helmet costs too much" as the reason they had not bought a helmet (36% vs 39% college graduates; OR = 0.9; 95% CI; 0.6, 1.2).

Helmet Use by Children

Of the 223 children who reported owning helmets, 125 (56%) said that they wore their helmets the last time they rode their bicycles; the overall prevalence for helmet use among all bicycle owners was 13%. The most frequently cited reasons for not wearing helmets are shown in Table 2. Answers given by children who owned and did not own helmets were similar, except that owners, who had presumably worn their helmets at least once, more frequently judged them too uncomfortable to wear, and more often listed "forgot to wear." There was no statistically significant association between whether or not the child wore his helmet the last time he rode his bicycle, and the child's sex, the level of parental education, parental health- or safety-related behavior, or parent's belief in the likelihood of bicycle injury or the ability of helmets to

Table 2.—Prevalence of Children's Reasons for Not Wearing Bicycle Helmets

Reasons	No. (%) of Owners (n = 98)	No. (%) of Nonowners (n = 694)
Friends don't wear helmets	27 (28)	173 (25)
Didn't think about it	16 (16)	159 (25)
Uncomfortable Don't see a	41 (42)	86 (12)
need Forgot	13 (13) 34 (35)	64 (9) 7 (1)
Unattractive	2 (2)	11 (2)

prevent these injuries.

COMMENT

This study provides potentially useful information on the factors that must be addressed by programs seeking to increase bicycle helmet use by children. The reasons given most frequently by parents for not purchasing bicycle helmets involved lack of awareness of their importance, which was also the reason perceived as most significant by the majority of physicians in the 1986 study by Weiss and Duncan. 17 This suggests that educational campaigns targeted at parents and focusing on the incidence and consequences of bicycle crashes and the effectiveness of helmets in preventing head injuries might substantially increase helmet ownership among children. The smaller proportion of parents who listed "never thought about purchasing" in the second half of the survey compared to the first half may reflect modest effects from the limited educational activities initiated in 1987. Since helmet ownership decreased markedly with decreasing levels of parental education, a primary target of educational programs must be families living in areas with low average levels of education. However, as even highly educated families had ownership rates of less than 50%, any such interventions should be community wide.

Although this survey did not collect information on helmet type or brand, other studies^{14,15} have reported that the majority of helmets used by both children and adults are hard shells with polystyrene liners, which provide the best head protection in laboratory test-

ing. 10 Educational programs to increase helmet use must emphasize that to ensure adequate protection, helmets purchased for children should meet the safety standards published by the American National Standards Institute

High cost appeared to be a significant deterrent to ownership. American National Standards Institute-approved helmets cost from \$25 to \$40 or even more for some models. Substantial increases in helmet ownership may depend on some reduction in cost, either directly by manufacturers because of supply and demand or indirectly through subsidized discount coupons, insurance coverage, or development of loan programs of the type used successfully with infant car seats.

Many parents also mentioned the child's refusal to wear a helmet as a major obstacle to helmet purchase; this perception seems accurate based on the comments of the children themselves. Neither parental education nor behavior and attitudes apparently influenced the child who owned a helmet to wear it. As with their parents, lack of awareness was commonly cited. However, peer pressure seemed to be the dominant influence, as the most frequently given reason for not wearing helmets was that friends did not wear them. To encourage more children to wear helmets, educational programs must address not only knowledge and awareness, but also the issue of peer pressure.

Another impediment to helmet use was discomfort, especially among those who already owned helmets. Discussions with manufacturers may be appropriate to encourage the redesigning of helmets to make them more comfortable for and attractive to children.

The principal limitation of this study is the potential bias caused by the response rate of 49%. We found little difference between respondents and non-respondents in age or sex, and the proportions of respondents reporting bicycle ownership (88%) was consistent with ownership rates reported previously. However, there were differences between respondents and nonrespondents in our proxy measures for socioeconomic status (zip code median income and proportions of high school graduates). These measures suggest a

self-selection bias toward families of higher socioeconomic status. Parental educational achievement clearly influenced the reasons parents gave for not purchasing helmets. Had there been a higher response rate from less-educated families, our data suggest that the reason "never thought about purchasing" would have been chosen by an even greater percentage of parents. On the other hand, parental education had no association with whether the child actually wore a helmet; our finding that only half of children who owned helmets actually wore them is therefore unlikely to have been biased by the low response rate from families of low socioeconomic status.

Our study found a higher prevalence of helmet use (13%) than the 3% to 4%

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use encountered in previous studies. 15,16 This may be because our estimate was based on reported use rather than direct observations as in the other reports. Studies^{22,23} of seat belt use have shown that reported use tends to be substantially higher than observed use; the same may be true for bicycle helmets. In support of this possibility, direct observations of school-age children observed riding bicycles in Seattle in September 1987 revealed that only 5.5% wore helmets.18 Even this lower figure of 5.5% suggests that helmet use may also be more common in Seattle than elsewhere. Finally, as noted in the previous paragraph, results from the present survey are likely to overestimate helmet use in Seattle because the survey respondents were more likely to be from

better-educated families, who were in turn more likely to have purchased helmets for their children. Even among the most highly educated families, however, only 43% reported having purchased helmets and just half of those children who owned helmets reported using them, suggesting that barriers to the purchase and use of helmets exist at all socioeconomic levels. The results of this study therefore provide a useful starting point for communities developing programs to increase bicycle helmet use by children.

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Lacerations in Urban Children

A Prospective 12-January Study

M. Douglas Baker, MD; Steven M. Selbst, MD; Michael Lanuti

 We prospectively investigated the epidemiologic characteristics of all lacerations (N = 2834) repaired at the Children's Hospital of Philadelphia (Pa) during 1987 and identified common hazards and possible avenues of intervention. Two-year-old children incurred most injuries; males outnumbered females 2:1. Almost two thirds (61.8%) of all lacerations occurred from May through September, and 62.2% between 3 and 9 PM. Most injuries occurred indoors (47.0%), on the sidewalk or street (22.5%), or in the residential yard (13.0%). Injuries usually occurred during play (42.3%) or daily activity (32.1%); 1247 (44.0%) involved some sort of fall. Vectors most frequently causing injury were broken glass bottles (15.0%), wooden furniture (12.0%), and asphalt or concrete (11.0%). Broken glass bottles also most frequently inflicted injuries resulting in functional impairment (0.2%), hospitalization (0.9%), or both. Complications were seen in 8% of all lacerations. Our data confirm the importance of injuryprevention strategies aimed at reduction of discarded glass objects (ie, recycling legislation), improved furniture design, and improved municipal services (ie, street repair).

(AJDC. 1990;144:87-92)

L acerations occur commonly in child-hood and represent approximately 30% to 40% of all injuries for which care is sought in a pediatric emergency department. ^{1,2} Estimates of national annual rates of laceration are 50 to 60 per 1000 children. ^{3,4} Overall, lacerations are the most common single type of child-

hood injury requiring evaluation by a physician.

Despite the frequency of lacerations, few reports have described the epidemiologic characteristics of their occurrence. Analysis has been limited to rate of occurrence¹⁴ or to specific subgroups of injuries (eg, glass-related injuries). Furthermore, most of these data are between 10 and 20 years old.

We analyzed prospectively the epidemiologic characteristics of lacerations in urban children. In doing so, we identified areas of possible preventive intervention.

PATIENTS AND METHODS

All children younger than 18 years who were brought to the Children's Hospital of Philadelphia (Pa) emergency department from January through December 1987 for evaluation and treatment of lacerations due to causes other than bites were prospectively enrolled in the study. Children's Hospital serves as both a primary-care center for indigent urban children, and as a level I pediatric trauma referral center for Philadelphia and surrounding counties.

Detailed six-page questionnaires were completed by the attending physicians at the initial visit. Missing historical or demographic information was obtained by the investigators (via telephone) on the day following the initial visit. Information collected included demographic data, time of injury, area of occurrence, activity during injury, presence and type of fall, causative agent, body part involved, size and depth of laceration, complicating factors, method of treatment, need for specialty service consultation, and disposition.

Follow-up information was collected from the parents by the investigators by telephone within 14 days of the initial visit and at the time of any revisit to Children's Hospital of Philadelphia. Information regarding suture removal, complications after repair, functional impairment, and duration of hospitalization (when applicable) was obtained then. Patients who were not available by telephone were contacted through their

identified primary care providers or by mail. As a method of cross-checking enrollment and data collection, all emergency department charts were reviewed daily by a single investigator (M.D.B.). Missing data were eliminated in this way. All data were entered into a computer and analyzed using SPSS. Patient treatment was completely unaffected by the study. Informed consent from patients or parents was not required by the Institutional Review Board.

RESULTS

A total of 2834 patients were enrolled during the study period. These children represented 4.4% of all visits to the Children's Hospital of Philadelphia emergency department in 1987. Males incurred the majority (68.3%) of lacerations. Most (86%) of the children were black, 12% were white, and 2% were either Asian or Hispanic. This reflects the racial distribution of those who use the emergency department.

The age distribution of injured children is shown in Figs 1 and 2. A marked increase in occurrence was noted after 7 months of age, a peak at 2 years of age, and a gradual decline thereafter. Fifty percent of all lacerations involved children 5 years old or younger.

The frequency of occurrence of lacerations varied both by month (Fig 3) and by time of day (Fig 4). Almost two thirds (61.8%) occurred during the warm-weather months of May through September. The majority (62.2%) of lacerations were incurred between the hours of 3 and 9 PM, with a peak at 8 PM. No significant seasonal variability was apparent in relation to time of day of injury.

Few children had significant delays in seeking medical care. Forty-six percent sought care within 1 hour of injury, 70% within 2 hours, and 96% within 8 hours. Factors associated with delay in care beyond 8 hours included private fee-forservice insurance carrier (P < .001), oc-

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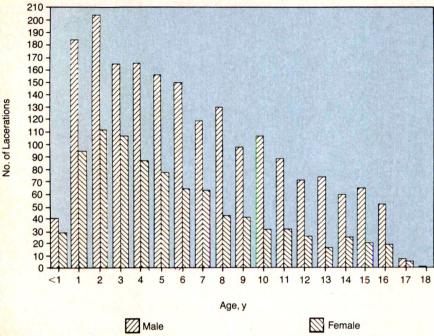


Fig 1.—Occurrence of lacerations according to age in years (n = 358).

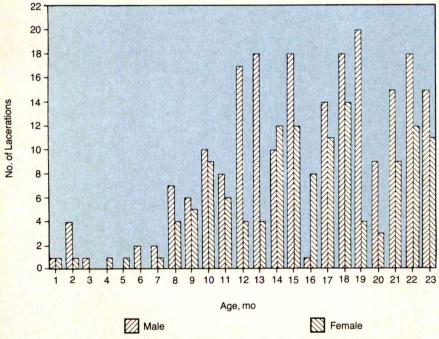


Fig 2.—Occurrence of lacerations in children younger than 2 years.

currence of injury between 2 and 9 AM (P<.001), injuries involving the genitalia, foot, wrist, or dorsum of the hand (P<.001), length of laceration less than 1 cm (P<.05), and partial-thickness depth of laceration (P<.01). All 22 lacerations with infection noted at the first

visit occurred in patients whose initial medical care was delayed 18 hours or more from the time of the injury.

Table 1 lists the various environmental locations where lacerations were inflicted. The most common sites were the home (indoors, 47.0%), the street or

sidewalk (22.5%), and the residential yard (13.0%). Within the home, lacerations most commonly occurred in the living room (25.2%), bedroom (22.3%), kitchen (18.6%), and hallway (14.4%). Lacerations occurring in the kitchen most commonly involved children older than 10 years (P<.0001), while those in the living room more often involved children younger than 11 years (P<.001). Otherwise, the age of the child played no role in the location within the home where the injury took place.

The activities in which children were engaged when they were injured are listed in Table 2. Play (42.3%) and daily activity (32.1%) most commonly preceded injury. Fighting (7.2%), bicycling (5.0%), and sports activities (3.6%) also accounted for significant proportions of the total, while suspected child abuse and neglect were identified in only 21 patients (0.7%). Forty-one (1.4%) of the children received lacerations while they were pedestrians or occupants of cars involved in motor vehicle accidents. Two of the 10 passenger-patients were wearing restraints when injured; neither required admission to the hospital.

Almost half (44.0%) of all lacerations were caused by falls (Table 3). Forty different types of scenarios led to these injuries; more than half resulted from five common occurrences. Most often, falls occurred on stairs (14.0%) and uneven pavement or sidewalks (10.7%) and from beds (10.3%), bicycles (9.5%), or chairs (8.4%). A misstep while running or walking on a smooth surface accounted for another 14.8% of lacerations.

More than 100 different objects were identified as lacerating vectors (Table 4). Of these, three categories of items (broken bottles, 15.0%; wooden furniture, 12.0%; and asphalt or concrete, 11.0%) inflicted over one third of all lacerations reported. Coffee tables accounted for one fourth of all wood-furniture injuries. Age is compared with injury by different materials in Table 5. Items not listed affected all ages equally.

The body parts injured are indicated in Table 6. The head was affected in 59.4% of lacerations; the upper extremities, 23.2%; the lower extremities, 15.0%; and all other areas, 2.3%. The body part injured was skewed by age.

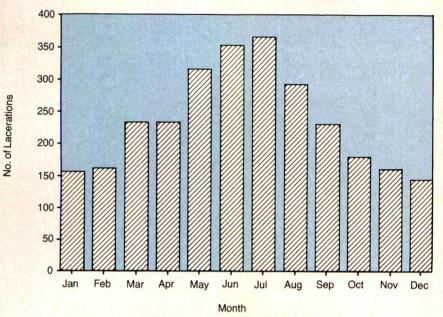


Fig 3. — Occurrence of lacerations according to month of year (N = 2834).

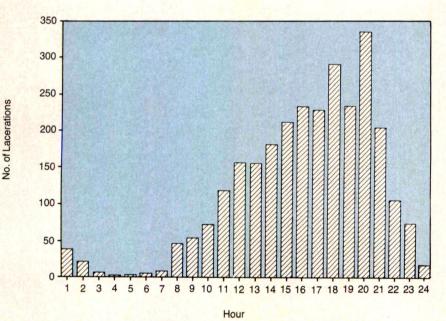


Fig 4. — Occurrence of lacerations according to time of day (N = 2834).

Of the 358 lacerations occurring in children younger than 2 years, 335 (93.6%) involved either the head or hand. The number of head lacerations in this group (N=271) was proportionately greater than in older children (P<.001). Although finger injuries were common in all ages, those involving either the dorsum or palm of the hand were more frequent in children older than 2 years (P<.01). Knee and foot injuries were

also more common in children older than 2 years (P<.01 and P<.001, respectively). Children with injuries of the dorsum or palm of the hand, the lower arm, wrist, and knee required hospitalization proportionately more often than those involving other body parts (Table 7). Conversely, children with head injuries were hospitalized less frequently than expected.

Most lacerations were full thickness

Table 1.—Area Wh	
Location	Laceration Frequency (%)
Indoors	
Home (all rooms)	1331 (47.0)
Living room	336
Bedroom	297
Kitchen	247
Hallway	192
Bathroom	57
Other	164
Unknown	38
School	105 (3.7)
Store	27 (1.0)
Day-care	23 (0.8)
Other	62 (2.3)
Outdoors	
Street, sidewalk	639 (22.5)
Residential yard	370 (13.0)
Playground, park	140 (4.9)
School yard	77 (2.7)
Sports facility, pool	28 (1.0)
Other	26 (0.9)
Unknown	6 (0.2)
Total	2834 (100.0)

Activity	Laceration Frequency (%)	
Play	1200 (42.3)	
Daily activity	910 (32.1)	
Fight	203 (7.2)	
Bicycling	141 (5.0)	
Team sports	102 (3.6)	
Housework	72 (2.5)	
Sleep	43 (1.5)	
Motor vehicle	38 (1.3)	
Child abuse	21 (0.7)	
Fire-hydrant play	18 (0.6)	
Skateboarding	17 (0.6)	
Roller or ice skating	16 (0.6)	
Other	43 (1.5)	
Unknown	10 (0.4)	
Total	2834 (99.9)*	

^{*}Total does not equal 100% due to rounding.

(76.5%) and 1.0 to 2.5 cm in length (55.9%) (Table 8). Of all injuries, 8.4% (239/2834) had complications on initial evaluation; most common was the presence of a foreign body (23.0%). Other complications included fractures (18.4%), arterial injury (18.0%), amputation (13.4%), infection (9.2%), and injuries to tendons (8.8%), muscles (4.2%), nerves (2.9%), and joints (2.1%).

Eighty-six (3.0%) of the patients required admission to the hospital. The mean duration of hospitalization was 2.7 days (range, 1 to 14 days; mode, 2 days). Children were more likely to be admitted if they incurred larger wounds (wound length <2.5 cm, 1.4% admitted;

Fall Circumstances	Laceration Frequency (%)
Stairs	174 (14.0)
Uneven pavement	133 (10.7)
Bed	129 (10.3)
Bicycle	119 (9.5)
Chair	105 (8.4)
Tripped	
Running	97 (7.8)
Walking	88 (7.0)
Hole or ditch	72 (5.8)
Playground equipment	55 (4.4)
Other furniture	34 (2.7)
Fence	31 (2.5)
Bathtub or shower	27 (2.2)
Scooter	20 (1.6)
Slippery surface	19 (1.5)
Other toy vehicle	16 (1.3)
Toilet	14 (1.1)
Skateboard	13 (1.0)
Other	101 (8.1)
Total	1247 (99.9)*

^{*}Total does not equal 100% due to rounding.

2.5 to 5.0 cm, 6.5% admitted; >5.0 cm, 15.4% admitted), were involved in a motor-vehicle accident (15 patients [39.5%] admitted), or suffered any one of the previously mentioned complications (59 patients [24.7%] admitted). Children with lacerations caused by glass and metal required hospitalization most frequently, 30.2% (n=26) and 29.1% (n=25), respectively. Lacerations from glass bottles were the single most common injury that led to hospitalization, accounting for 18.6% (n = 16) of the total admissions. Injuries following falls resulted in 28 admissions (32.6% of the total). The most common falls leading to admission were those on uneven pavement (5.3%; 7/133), into a hole or ditch (5.6%; 4/72), or while running or walking on a smooth surface (2.2%; 4/185).

Functional impairment at the time of follow-up examination occurred in 18 (0.6%) of the children. Thirteen (72.2%) of these children were 8 years of age or older; none was younger than 2 years. Glass injuries of the hand accounted for one third of this group. The remainder were caused by metal objects in 5 patients, auto parts in 2 patients, fan blades in 2 patients, rocks in 2 patients, and ice in 1 patient. The most common functional impairment was decreased range of motion of a large joint (ie, knee, wrist, or elbow), which occurred in 6 patients. Other impairments included decreased ability to oppose the thumb in 3 patients, finger amputation in 3, mus-

Table 4. - Material Causing Laceration Laceration **Material** Frequency (%) Glass 424 (15.0) Broken bottle 53 (1.9) Window Drinking glass 49 (1.7) 34 (1.2) Storm door 23 (0.8)Furniture 18 (0.6) Novelty item, ornament 14 (0.5) Mirror Other 25 (0.9) Miscellaneous 312 (11.0) Asphalt or concrete 91 (3.2) 35 (1.2) Stone or rock Earth or turf Wall 33 (1.2) Fist 25 (0.9) 25 (0.9) Linoleum floor Bathtub 18 (0.6) Ice or snow 16 (0.6) Tile floor 14 (0.5) Other 66 (2.3) Wood **Furniture** 341 (12.0) 105 (3.7) Door Stairs 77 (2.7) Twig or stick 36 (1.3) 26 (0.9) Floor 30 (1.0) Other Metal Knife blade 78 (2.8) **Furniture** 70 (2.5) (2.4)Auto part 61 (2.2) Tov Fence or gate 66 (2.3) Radiator (1.6)45 (1.6) Pole 42 (1.5) Tool 41 (1.4) Can 40 (1.4) Nail 36 (1.3) Railing Playground equipment 29 (1.0)28 (1.0) **Appliance** Razor blade 21 (0.7)Bike pedal 21 (0.7) Jewelry 14 (0.5) Fan blade 11 (0.4) Other 120 (4.2) Plastic 25 (0.9) Toy **Furniture** 23 (0.8) Television or radio 13 (0.4) Other 36 (1.3) Unknown 10 (0.4)

*Total does no	equal 100	0% due to	rounding.
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2384 (99.9)*

Total

Material Causing Injury	Most Commonly Affected Age Range
Metal can	13-18 mo
Stairs	12 mo-4 y
Wooden furniture	13 mo-6 y
Asphalt or concrete	13 mo-9 y
Glass bottle	17 mo-11 y
Bathtub	2-4 y
Drinking glass	2-5 y
Metal furniture	2-6 y
Toy	2-6 y
Radiator	2-6 y
Playground equipment	2-6 y
Appliance	2-9 y
Fence	4-11 y
Twig or stick	4-11 y
Rock or stone	5-7 y
Storm door	5-12 y
Ice or snow	7-10 y
Knife blade	9-16 y
Fist	12-16 v

Table 6.—Body Part Lacerated		
Body Part	No	. (%)
Head		
Eye	3	(0.1)
Face	1052	(37.1)
Mouth	285	(10.0)
Scalp	344	(12.1)
Neck	2	(0.1)
Trunk		
Abdomen	7	(0.2)
Chest	24	(0.8)
Upper extremity		
Finger	348	(12.3)
Hand	170	(6.0)
Lower arm, elbow, wrist	116	(4.1)
Upper arm, shoulder	23	(0.8)
Lower extremity		
Foot	138	(4.9)
Lower leg, knee, ankle	206	(7.3)
Toe	40	(1.4)
Upper leg	40	(1.4)
Buttocks	9	(0.3)
Genitalia	27	(1.0)
Total		(99.9)*

^{*}Total does not equal 100% due to rounding.

cle weakness due to denervation in 2, decreased sensation distal to the injury in 2, decreased visual acuity in 1, and formation of a cosmetically deforming facial scar in 1.

COMMENT

Our data confirm that lacerations are common injuries in young urban children. They represent 4.4% of all emergency department visits at our institution and are reportedly among the most common injuries for children younger than 17 years. ¹⁴ Although several patients older than 16 years were enrolled in the study, these occurrences were not thought to be representative of this age group as a whole. A significant portion of patients of this age receive their care at adult emergency facilities.

We observed some interesting epidemiologic trends in our study population. Lacerations most commonly involved younger children who lack the experi-

Table 7.—Need for Hospitalization According to Body Part*			
Body Part Injured	% of Total Lacerations (N = 2834)	% of Total Admissions (n = 86)	Significance
Head	60	35	P<.0001
Hand (dorsum, palm)	6	13	P<.01
Finger	12	16	NS
Lower arm, wrist	3	9	P<.001
Knee	4	10	P<.001
Foot	6	3	NS
Other	9	13	NS

^{*}Percentages do not total 100% due to rounding. NS indicates result was not significant.

Laceration Characteristic	Total No. (%)*	No. (%) Admitted
Size, cm		
<1.0	638 (22.5)	9 (1.4)
1.0-2.5	1584 (55.9)	24 (1.5)
2.6-5.0	463 (16.3)	30 (6.5)
>5.0	149 (5.2)	23 (15.4)
Thickness	THE RESERVE OF THE PARTY AND THE	CANADA SERVICIO DE LA COMPANSIONE DE L
Partial	665 (23.5)	5 (0.8)
Full	2169 (76.5)	81 (3.7)

^{*}Total does not equal 100% due to rounding.

ence, common sense, and motor coordination of older children. This has also been observed in several other types of childhood injuries, including electrical injuries, foreign-body-related injuries, the downings, and unintentional ingestions. Likewise, the 2:1 male-to-female sex ratio is consistent with other childhood injury studies. Likewise, 1,3,4,9-14

We observed a definite seasonal occurrence of lacerations. As is the case for other injuries that depend on the degree of physical activity of the host (ie, animal and human bites 15,16), lacerations were most common during warmweather months. More than two thirds (68.0%) of outdoor injuries occurred from May through September, as opposed to 44.3% of all indoor injuries. This excess of lacerations occurring outdoors during warm weather was directly attributable to outdoor activities such as bicycling, swimming, baseball and other field sports, skateboarding, swimming, play in fire-hydrant spray, and other outdoor play. The hour of injury is skewed toward those times when children have maximum physical activity and, presumably, least supervision. 9,16 During later hours, increased fatigue and decreased coordination might also be contributory factors.

As one might expect, delay in seeking care was more common for smaller wounds involving cosmetically unimportant areas and those occurring during inconvenient (ie, early morning) hours of the day. Interestingly, a significantly higher proportion of patients with private-insurance carriers delayed care beyond 8 hours, compared with children with all other modes of payment, including self-pay and medical assistance. The reason for this occurrence is unclear.

Our data support the findings of others^{11,17} that most injuries take place where children spend the most active portions of their day. More than 47% of injuries in our study population took place in the home; for preschool children, the home accident rate was 67.3%. The child's home environment and/or their level of supervision is in great need of modification, given these rates, plus the occurrences in residential yards.

The playground has also been identified as a common site for childhood injury to occur. ^{17,18} In our study population, only 4.9% of all lacerations took place in

that setting. In the catchment area for our study population, lack of security and maintenance has eliminated the playground as a safe place for children to play. As a result, children may have shifted their activities to another hazardous environment of even greater concern. Almost 23% of the total lacerations occurred in the street or on the sidewalk. Of those, 20.8% resulted from tripping over uneven pavement, and 28.2% involved contact with broken (bottle) glass. Notably, pavement injuries were the largest single group of falls prompting admission to the hospital, and glass-related injuries resulted in a higher proportion of complications than any other category. These data indicate our need to face the realities of urban life and to construct safe, clean, supervised playgrounds for children to use. In addition, "street" injuries could be reduced through improved municipal services (ie, sidewalk repair) or through consumer or environmental legislation. Massachusetts recycling legislation led to a 60% reduction in glass-related lacerations in children in the course of 1 year.19

It is not surprising that most lacerations occurred during daily activity and play. What is of interest is the extremely low proportion of lacerations due to automobile accidents (1.4%) or to child abuse (0.7%). The latter represent approximately 6% of all physical-abuse cases seen in our emergency department during the study period. These findings demonstrate that blunt injuries are more common in these circumstances.

The high proportion (44.0%) of lacerations resulting from falls is consistent with the observations by others. 1,17,20 Our data emphasize the importance of four particular types of falls. Falls from furniture and bicycles and on stairs and uneven pavement accounted for more than half of all such lacerations. Previous reports of stairway,21 bicycle,14,22 and furniture injuries23 also cite lacerations among their most frequent injury types. The frequency of occurrence of these injuries underscores the importance of development of prevention strategies, such as bicycle-safety education14,22 and use of stairway entry gates.2 The fact that a disproportionately high number (83.0%) of all falls from furniture involved children younger than 6 vears reinforces the need for better parental supervision as well.

Finally, our data unequivocally identify several particularly hazardous vectors. Overall, broken glass, furniture, and concrete lead the list. However, within specific age groups, individual trends appear that seem to parallel the child's exposure. Toddlers learning to walk (between the ages of 12 and 23 months) frequently bump into furniture or fall onto stairs, concrete, or street glass. In addition to these hazards, preschoolers (between the ages of 2 and 6 years) are often injured by common household items such as radiators, drinking glasses, toys, and a variety of outdoor playground equipment. The frequency of injury from these objects gradually tapers in elementary-schoolage children (6 to 12 years old), only to be supplemented by those with which

- this age group, these are most commonly associated with injuries in adolescents.
 - Regardless of age-related trends, injuries due to street glass, low-level furniture, and concrete demand our attention. Not only are these objects associated with lacerations more commonly than others, but they are also among the leaders in cause of complications and need for hospitalization. In particular, it is essential that we recognize the substantial health hazard posed by the broken glass that litters our

interaction requires greater strength or

motor skills on the part of the host (ie,

injuries incurred on fences, storm

doors, tree parts, ice, and snow). Al-

though implements of violence (ie,

knives and fists) also begin to appear in

glass clean-up and sidewalk repair) has been previously stated. Improved furniture design (ie, rounded edges) and parental education has also been recommended.23 Finally, the role of the pediatrician in educating families about injury prevention cannot be overemphasized. The trends listed in Table 5 might help to guide pediatricians in their injury-prevention counseling of parents. A variety of office-based educational and interventional modes are available to the practitioner. 24 In addition, physician support of intelligent injury-prevention legislation and voluntary regulations is essential to the well-being of our children. Previous experience supports this approach. 19,25

This study was supported in part by the Children's Hospital Trauma Research Fund, Philadel-

Patricia Parkinson meticulously prepared the manuscript.

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Special Features

Radiological Cases of the Month

David W. Green, MD, Edward F. Donovan, MD (Contributors); Beverly P. Wood, MD (Section Editor)

A 1780-g white male neonate with severe fetal hydrops was delivered vaginally to a 38-year-old, blood type O positive, primigravida mother after 26 weeks of gestation. Prior to the onset of preterm labor, the pregnancy had been uncomplicated. Prenatal care included a sonogram and

amniocentesis at 15 weeks of gestation that revealed a fetal size consistent with dates and a 46, XY karyotype, respectively.

At birth, the infant was cyanotic with poor muscle tone and no respiratory effort. There was anasarca but no other obvious deformity. Resuscitation included tracheal intubation, bilateral chest tube placement, inotropic support, and vascular volume expansion. Apgar scores were 1 at 1 and 5 minutes (heart rate only), and 2 at 10 minutes (heart rate only).

Initial laboratory values included a hematocrit value of 0.60 and a white blood cell count of 12.1×10^{9} /L, with

12 neutrophils, 14 bands, and 3 metamyelocytes. The absolute neutrophil count was 3.5×109/L. The platelet count was 88×109/L. A venous blood gas sample 20 minutes after birth showed a pH of 6.98, a Pco2 of 17.6 kPa, a Pao, of 0.8 kPa, and a base deficit of 15. The infant's blood type was O positive. The direct Coombs' test was negative. An initial chest roentgenogram was obtained minutes after birth (Fig 1). The infant could not receive adequate ventilation, and respiratory failure was exacerbated by development of an air leak and pneumothoraces (Fig 2); he died shortly thereafter.

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Contributed from the Department of Pediatrics, Division of Neonatology, University of Cincinnati (Ohio) (Dr Green), and the Department of Pediatrics, Regional Center for Newborn Intensive Care, Children's Hospital Medical Center, Cincinnati (Dr Donovan).

Reprint requests to Department of Radiology, Childrens Hospital of Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90027 (Dr Wood).

Figure 1.

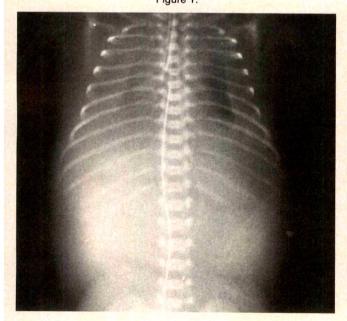
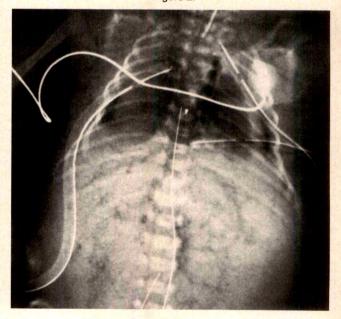


Figure 2.



Denouement and Discussion

Hydrops Fetalis With Pulmonary Hypoplasia

Fig 1.—Roentgenogram of chest and abdomen (recumbent) showing a "bell-shaped" thorax, an endotracheal tube in the right main-stem bronchus, small lung volume, bilateral pleural effusions, and anasarca.

Fig 2.—Roentgenogram of the chest and abdomen (recumbent) shortly before death of the infant showing pneumothoraces, pneumomediastinum, and gas throughout the abdominal vasculature.

Persistent inability to ventilate or oxygenate after intubation and thoracentesis is strongly suggestive of patients with pulmonary hypoplasia. The initial chest roentgenogram showed decreased lung volume and large pleural fluid collections. Respiratory failure was rapidly exacerbated by bilateral air leak and subsequent intravascular gas accumulation.

By chest roentgenogram, pulmonary hypoplasia is evident as decreased lung size despite high ventilatory distending pressures. Air leak results from overdistention of immature air sacs and bronchioles in hypoplastic lungs.

At autopsy, the lungs were extremely small and the combined wet weight was 10.8 g, more than 2 SDs less than the mean for control infants of less than 24 hours of age with respiratory distress syndrome and rupture of membranes.² These findings indicate pulmonary hypoplasia.

Swischuk et al³ have categorized the causes of bilateral pulmonary hypoplasia as idiopathic or as a result of fetal lung compression from an extrathoracic, thoracic, or intrathoracic source. In this case, pulmonary hypoplasia may have been related to compression of developing lung tissue by pleural fluid. Animal models have shown that artificial creation of intrathoracic space-occupying lesions can produce pulmonary hypoplasia. 4,5 The common occurrence of pulmonary hypoplasia in hydrops fetalis is attributed to the presence of fluid occupying potential lung growth space.6

The neonate sustained rapidly progressive barotrauma, manifested by pulmonary air sac rupture, pneumo-

thorax, and eventually massive intravascular gas (Fig 2). The intravascular gas was noted clinically as the child developed irregular bright red patches over the skin. Concomitantly, in confirming the proper connections of all intravascular catheters, gas was noted to bubble regularly from the umbilical artery catheter port as it was opened.

Massive intravascular gas can occur from direct vascular instillation of gas (eg, via an intravenous or intra-arterial catheter) or from a pulmonary bronchiolovascular fistula caused by rupture of an air space or bronchiole, or pulmonary instrumentation (eg, chest tube insertion). In this case, the intravascular gas was felt to be due to air sac-bronchiolocapillary or bronchovenous connection. Intravascular gas has been reported to accumulate spontaneously.

Radiographically, gas may be identified in both the arterial and venous circulations, including the heart. Systemic arterial gas is distributed after return to the left atrium from the pulmonary veins or via an atrial septal defect. Gas in the venous system can be due to direct introduction, or via retrograde flow (via a patent ductus arteriosus or a patent foramen ovale). Retrograde flow of gas (opposite of the flow of blood) has been attributed to the buoyancy of gas.9 Massive intravascular gas is almost always a preterminal event, with immediate mortality approaching 95%.10

The cause of nonimmune hydrops in this case was not determined. The causes of nonimmune hydrops are multiple and have been recently reviewed. 11,12 We postulate that the causal insult manifested itself between

the time of the normal ultrasound findings at 15 weeks and delivery at 26 weeks. Pulmonary hypoplasia can occur with as few as 6 days of oligohydramnios.² In this case, there was normal amniotic fluid volume and no evidence of hematological origin. Viral and bacterial cultures were negative. Furthermore, at autopsy, there was no evidence of cardiac, gastrointestinal, renal, or liver disease.

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Christopher J. Mehall, MD; Gary M. Amundson, MD (Contributors); Beverly P. Wood (Section Editor)

A male infant weighing 2700 g was born by cesarean section at 35 weeks' gestation to a 31-year-old gravida 6 para 5 mother who had an uncomplicated pregnancy.

At birth the infant was cyanotic and dysmorphic. An initial chest roent-genogram (Fig 1) and an echocardiogram were obtained. Echocardiography showed a dilated right atrium and biventricular enlargement with a large right-to-left ductal shunt.

Despite intense medical therapy, the infant's level of oxygenation deteriorated. In anticipation of beginning extracorporeal membrane oxygenation therapy, cranial ultrasonography was performed (Fig 2). Following ultrasonography a skull series was obtained (Fig 3).

Despite aggressive treatment the patient's condition worsened. Attempts at cardiopulmonary resuscitation provided only temporary improvement and he died within several hours.

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Contributed from the Department of Radiology, Children's Hospital of Michigan, Detroit.

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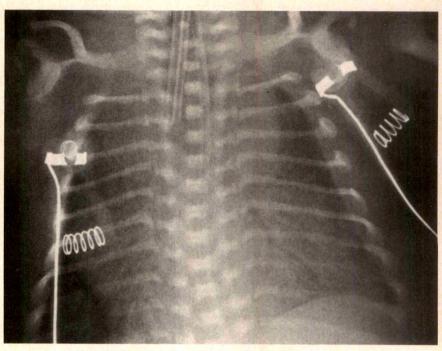


Figure 1.

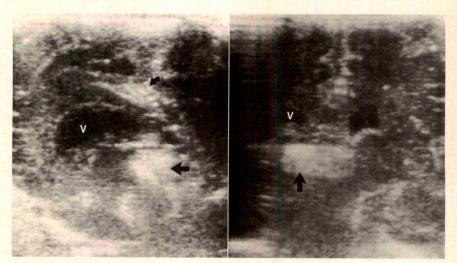


Figure 2.

The Editors welcome contributions to Picture of the Month and Radiological Case of the Month. Those who wish to contribute should send their manuscripts to Dr Feingold (Picture of the Month), National Birth Defects Center, Franciscan Children's Hospital, 30 Warren St, Brighton, MA 02135, or Dr Wood (Radiological Case of the Month), Department of Radiology, Childrens Hospital of Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90027. Articles and photographs accepted for publication will bear the contributors name. There is no charge for reproduction and printing of color illustrations.

Denouement and Discussion

Systemic Air Embolism Within a Vein of Galen Malformation

Fig 1.—Initial anteroposterior chest roentgenography demonstrates marked cardiomegaly. A ductus bump is present and the pulmonary vasculature is prominent and ill defined. A left pleural effusion is seen. Note the hypoplastic vertebrae and thinning of the clavicles and ribs.

Fig 2.—Cranial sagittal (left) and coronal (right) ultrasonography demonstrate a densely echogenic structure (straight arrow) posterior to the third ventricle, representing air within the vein of Galen malformation. Tubular areas of increased echogenicity (curved arrow), representing air in feeding vessels, are also seen. These large vessels demonstrated marked pulsatile activity during the real-time examination. V indicates the lateral ventricle.

Fig 3.—Frontal (left) and lateral (right) roentgenography of the skull demonstrate air within abnormal vascular structures in the midline (arrows). VG indicates the vein of Galen. Note the prominent brachycephaly and hypertelorism.

Arteriovenous malformations are not often considered a cause of severe cardiac insufficiency in a neonate. While rare, a vein of Galen malformation is the most common of such extracardiac shunts. In a study of 45 neonates with a vein of Galen malformation, 43 patients presented with congestive heart failure, 1 presented with obstructive hydrocephalus, and another patient presented with subarachnoid hemorrhage.

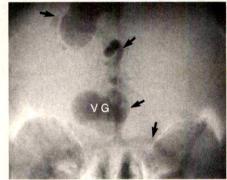
A vein of Galen malformation involves aneurysmal dilatation of the vein of Galen and straight sinus with direct, anomalous connection to any or all of the anterior, middle, and posterior cerebral arteries. Cranial ultrasonography reveals large pulsatile arterial vessels feeding into the region of the vein of Galen and straight sinus. Echocardiography will show signs of a large left-to-right shunt and rapid passage of contrast (air microbubbles) from the left side of the heart to the superior vena cava via the cerebral malformation, with dilated, hyperdynamic ventricles and absence of a major intracardiac defect.2

Eighty percent of cranial arteriovenous malformations involve the vein of Galen. The incidence in males predominates over females 6:1.3.4 These infants are severely cyanotic and tachypneic. Cerebral auscultation reveals a cranial bruit.

The prognosis for these patients remains poor. Therapeutic procedures on these children are possible only if there are single feeding and draining vessels. Even with therapy, early mortality for vein of Galen malformations ranges from 66% to 100%.³

This case was complex in that there was increased echogenicity in the region of the great vein of Galen. Such a malformation will typically show as a large, sonolucent, echo-free lesion with the appearance of a cystic mass.

Possible causes of this area of in-



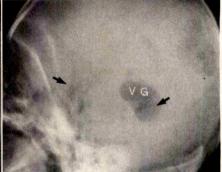


Figure 3.

creased echogenicity include edema and hemorrhage. Calcification, which has been noted in association with a vein of Galen malformation, either within vessel walls or in adjacent cerebral parenchyma, and thrombosis within a malformation, which may be associated with hemorrhagic infarction, can also appear highly echogenic.^{4,5}

The cause of the increased echogenicity on ultrasonography in this patient becomes apparent on inspection of the plain roentgenograms of the skull. Air, which is echogenic, is seen within the abnormal midline vascular malformation.

The occurrence of systemic air embolism is a rare complication in neonates treated with positive pressure ventilation therapy and is catastrophic. To our knowledge, there has been one reported case of patient survival; otherwise, all reported cases have been fatal.

The cause of such embolization is uncertain but may involve either alveolar, capillary, or bronchovenous fistulas following alveolar or air space rupture. This has been demonstrated to occur when intra-alveolar pressure exceeds the left atrial/pulmonary venous pressure, allowing air to enter the blood stream.^{6,7}

Autopsy results in this patient revealed that in addition to the vein of Galen malformation, the patient had spondyloepiphyseal dysplasia. No direct association is known between this type of dysplasia and the visualized vascular anomalies.

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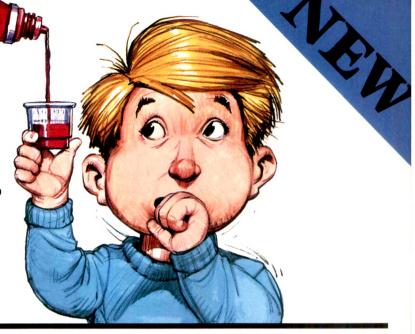
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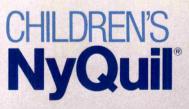
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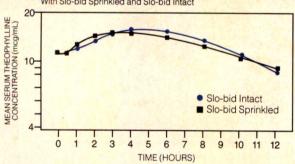
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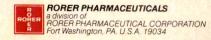
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24-hour dosing interval not selected patients (see 00.04 km 2 hour hard sold microation for description of appropriate patient population).

INDICATIONS AND USAGE: For relief and/or prevention of symptoms from asthma and reversible bronchospasm associated with chronic bronchist and emphysema associated with chronic bronchist and emphysema components of this product. It is also contraindicated in natients with active peptic uicer disease and in individuals with underlying setzure disorders (unless receiving appropriate anticonvulsant medication).

WARNINGS: Serum levels above 20. p/m, are rarely found after appropriate aministration of the recommended doses. However, in individuals in whom theophylline plasma clearance is reduced for any reason, even conventional doses. However, in individuals in whom theophylline plasma clearance is reduced from any reason, even conventional doses may result in increased serum levels and potential toxicity. Reduced theophylline clearance has been documented in the following readily identificable upon. I patients with impaired renal or liver function; 2) patients over 50 years of ale, particularly makes with characteristic plasmas over 50 years of ale, particularly makes with characteristic plasmas over 50 years of ale, particularly makes with characteristic plasmas over 50 years of ale, particularly makes with characteristic plasmas over 50 years of ale, particularly makes with characteristic plasmas over 50 years of ale, particularly makes with characteristic plasmas over 50 years of ale, particularly makes with characteristic plasmas over 50 years of ale, particularly makes with characteristic plasmas over 50 years of ale, particularly makes with characteristic plasmas over 50 years of ale, particularly makes over 50 years of ale, particularly makes over 50 years of ale, particularly makes over 50 years 5

resourction or gosage and aboratory monitoring is especially appropriate in the above individuals. Serious side effects such as ventricular arrhythmias, convulsions, or even death may appear as the first sign of toxicity without any previous warning. Less serious signs of theophylline toxicity (i.e., nausea and restlessness) may occur frequently when initiating therapy but are usually transient; when such signs are persistent union maintenance therapy, they are often associated with serious concentrations above 20 µg/ml. Stated differently, serious toxicity is not reliably proceeded by less series side effects. A serum concentration measurement is the only reliable method of identifying a potential for life-threatening toxicity.

Many patients who require theophylline exhibit tachycardia due to their underlying disease process, so the cause/effect relationship to elevated serum theophylline concentrations may not be appreciated. Theophylline products may cause dysrhythmia and/or worsen preexisting arrhythmias and any significant change in rate and/or rhythm warrants monitoring and turther investigation.

rate and/or hythm warrants monitoring and further investigation.

Studies in laboratory animals fiminigings, nodents, and dogs) recorded the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta agonists and methylxanthines were administered concurrently. The significance of these findings when applied to humans is currently unknown.

PRECAUTIONS: General: On the average, theophylline hall-life is shorter in cigarette and marijuana smokers than in nonsmokers, but smokers can have half-lives as long as nonsmokers. Theophylline should not be administered concurrently with other arnthine preparations. Use with caution in patients with typozemia, hypertension or with a history of peptic ulear. Theophylline may occasionally act as a local intrinant to the Git tact, although GI symptoms are more commonly centrally mediated and associated with serum drug concentrations over 20 µg/m.

Information for Patients:

The physician should reinforce the importance of taking only the prescribed dose at the prescribed time intervals. The physician should reinforce the importance of taking only the prescribed when the physician is symptoms occur repeatedly, especially near the end of a dosing interval. When prescribing administration by the sprinkle method, details of the proper technique should be explained to the patient.

The prescribing administration by the sprinkle method, details of the proper technique should be explained to the patient.

prescribing administration by the sprinkle method, details of the proper feeningle should be explained to the patient. **Laboratory Test:** Serin levels should be monitored periodically to determine the theophylline levels associated with observed clinical response and to identify the potential for loxicity. For such measurements, the serum sample should be obtained at the time of peak concentration, approximately 5-9 hours after the moniting dose. It is important that the patient has not missed or taken additional doses during the previous 48 hours and that dosing intervals have been reasonably equally spaced.

ORGER DIRECTURE OF SECRET SECRET

DOSE ADJUSTMENT BASED ON SERUM THEOPHYLLINE MEASUREMENTS WHEN THESE INSTRUCTIONS HAVE NOT BEEN FOLLOWED MAY RESULT IN RECOMMENDATIONS THAT PRESENT RISK OF TOXICITY TO THE PATIENT.

Trug Interactions:
Drug-Drug: Toxic synergism with ephedrine has been documented and may occur with some other sympathomimetic broncholidators. In addition, the following drug interactions have been demonstrated:

Theophylline with: Allopurinol (high dose) Increased serum theophylline levels Increased serum theophylline levels Cimetidine Erythromycin, Troleandomycin Increased serum theophylline levels Increased renal excretion of lithium Lithium carbonate

Oral contraceptives Increased serum theophylline levels Decreased theophylline and phenytoin serum levels
Decreased serum theophylline levels Phenytoin Rifampin

Rifampii Drug-Foot: Taking Slo-bid immediately after a high-fat content meal such as 8 ounces whole milk. 2 fred eggs 2 strips bacon, one bran muffin with butter, 2 ounces hash brown potatoes (about 789 calories, including approximately 49 gm of fatl may result in a decrease in the rate of absorption, but with no significant difference in the extent of absorption (about 789 calories), and the extent of absorption (about 789 calories). The influence of the type and amount of other foods, as well as the time interval between drug and food, has not been studied.

Drug/Laboratory Test Interactions: Currently available analytic methods, including high-pressure liquid chromatography and immunosasy techniques, for measuring serum theophylline levels are specific. Metabolites and other drugs generally do not affect the results. Other new analytic methods are also now in use. The physician should be aware of the laboratory method used and whether other drugs will interfere with the assay for theophylline.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term carcinogenicity studies have not been performed with theophylline.

performed with recognitude.

Chromosome-breaking activity was detected in human cell cultures at concentrations of theophylline up to 50 times the therapeutic serum concentrations in humans. Theophylline was not mutagenic in the dominant lethal assay in male mice given theophylline intrapertioneally in doses up to 30 times the maximum daily human oral dose. Studies to determine the effect on fertility have not been performed with theophylline.

Pregnancy: Pregnancy Category C— Animal reproduction studies have not been conducted with theophylline. It is also not known whether theophylline can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Theophylline should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Theophylline discount or great to a program manner in clearly necessary necessary.

Nursing Mothers: Theophylline is distributed into breast milk and may cause intribuility or other signs of toxicity in nursing infants. Because of the potential for serious adverse reactions in nursing infants from theophylline, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:

- Safety and effectiveness of Slo-bid Gyrocaps administered:

 1. Every 24 hours in children under 12 years of age, have not been established.
- 12 hours in children under 6 years of age, have not been established.

ADVERSE REACTIONS: The following adverse reactions have been observed, but there has not been enough systematic collection of data to support an estimate of their frequency. The most consistent adverse reactions are usually due to overdosage.

usually use to declosage, to describe the described by th

Cardiovascular, palpitation, tachycardia, extrasystoles, flushing, hypotension, circulatory failure, ventricular arrhythmias.

Respiratory: tachypnea

Other: alopecia, hyperglycemia, inappropriate ADH syndrome, rash

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription. Keep this and all medications out of the

HOW SUPPLIED: Slo-bid Gyrocaps are identified as follows

HOW SUPPLIED: Slo-bid Gyrocaps are identified as follows:

50 mg — Clear (cap) and opaque white (body) capsule with 50 printed in red
75 mg — Opaque white (cap) and opaque white (body) capsule with 75 printed in red
100 mg — Clear capsule with 100 printed in red
125 mg — Opaque white (cap) and opaque white (body) capsule with 125 printed in red
200 mg — Opaque white (cap) and clear (body) capsule with 200 printed in red
300 mg — Opaque white (cap) with 300 printed in red
300 mg — Opaque white (cap) with 300 printed in red
Slo-bid Gyrocaps 50 mg are available in bottles of 100 (NDC 0075-0057-00), bottles of 1000 (NDC 0075-0075-00)
(NDC 0075-1075-00), bottles of 1000 (NDC 0075-1075-99) and in unit dose 10 x 10 (NDC 0075-0076-02), slo-bid Gyrocaps 100 mg are available in bottles of 1000 (NDC 0075-1070-99) and in unit dose 10 x 10 (NDC 0075-0070-09)



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Sports Medicine

William B. Strong, MD, Augusta, Ga Carl L. Stanitski, MD, Pittsburgh, Pa Ronald E. Smith, PhD, Seattle, Wash Jack H. Wilmore, PhD, Austin, Tex



Purpose.—This section provides current information related to the medical needs of young athletes, as pertinent to counseling young athletes and their parents regarding sports participation and practices contributing to the health maintenance of the athlete, as well as current concepts in the prevention, diagnosis, and treatment of sports-related illnesses and injuries.

Editorial Comment.—The authors provide further documentation in the rapidly developing literature concerning anabolic steroid abuse in the adolescent population. Pediatricians and health care providers must become aware of the magnitude of the problem and its health consequences. At a minimum we have a responsibility to educate all of our patients to the hazards of all illicit agents and the problems of substance abuse. The legacy of the Woodstock generation reads like a Who's Who of drugrelated deaths—the impact of anabolic steroids may not be quite as spectacular as heroin and cocaine, but it is a sign of a vast underlying problem in today's society.—W.B.S.

The Use of Anabolic Steroids in High School Students

Rise Terney, MA, Larry G. McLain, MD

. The use of anabolic steroids by athletes has been a frequent topic in many recent reports. While much has been written in the lay literature, there is little in the scientific literature documenting the actual use of steroids, particularly in adolescents. We describe the results of a survey of 2113 high school students. The survey was designed to elicit information about students' general knowledge about anabolic steroids, awareness of the risks and side effects, and the incidence of use of anabolic steroids. Ninety-four (4.4%) of 2113 students admitted using anabolic steroids. Broken down by sex, 67 (6.5%) of 1028 males and 27 (2.5%) of 1085 females were users of steroids. Athletes had a higher use of steroids (79 [5.5%] of 1436 subjects) than nonathletes (15 [2.4%] of 636 subjects). These data suggest that we have another serious, as yet unappreciated drug problem in our adolescents.

(AJDC. 1990;144:99-103)

The subject of anabolic steroid use by athletes has received a great deal of publicity recently in the lay press. The most sensational story involved Canadian Olympic sprinter Ben Johnson, who set a world record in the 100-m dash and then had test results positive for steroids and was stripped of his Olympic gold medal (USA Today, September 27, 1988, sports section, p 1). Another story about college football in Sports Illustrated (October 24, 1988:82-102) documented a chilling tale of the side effects of anabolic steroids. In this article it was reported that steroids are widely used by athletes seeking an increase in muscle size and strength. In 1983, 15 athletes were disqualified from the Pan-American games for using anabolic steroids, and in the same year the National Collegiate Athletic Association conducted its first survey of usage of drugs and alcohol among college football players. In 1986 the NCAA began random drug screening of athletes who were on national championship teams. The National Football League has recently announced a new testing program for anabolic steroids (New York Times, October 26, 1988, sports section, p 39).

While much of the current publicity may seem to indicate recent trends, in 1973, the American Academy of Pediatrics was concerned about the dangers of anabolic steroids, stating that the use of androgenic-anabolic steroids is contraindicated during adolescence.2 Four years later the American College of Sports Medicine formally opposed the use of anabolic steroids.3 The dangers of anabolic steroids have been reviewed in several publications. 4-10 In spite of these early warnings, the use of anabolic steroids appears to be on the rise. This may be due in part to a subtle, steady shift away from an emphasis on sports being an educational and growth experience for young children to an emphasis only on winning.

While much has been written in the lay literature suggesting a significant increase in the use of anabolic steroids, recent medical studies about anabolic steroids have dealt primarily with adults. There is little documentation in the scientific literature about the incidence of anabolic steroid use in adolescents. This study documents the results of a questionnaire administered to high school students regarding anabolic steroid use. We believe this is the first

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Reprint requests to Parkside Sports Medicine Center, 1825 Dempster St, Park Ridge, IL 60068 (Dr McLain). report detailing the actual incidence of use of these drugs in this population.

METHODS

The high school in this study is located in a suburb of Chicago; 3047 students attend the 4-year school. One of the authors (L.M.) has been a team physician at the school for several years and established an effective working relationship with the school's two athletic directors. When the idea of surveying the students about anabolic steroids was presented to the athletic directors, they were enthusiastic about the project and were highly supportive.

A 29-question survey was designed by the authors (Fig 1). The questionnaire was designed to elicit information about students' general knowledge about anabolic steroids, awareness of the risks and side effects, perceptions of use by others, actual incidence of use of anabolic steroids, how and where users obtained the steroids, and information about use by student-athletes in different sports.

The survey was given to the students on one day in May 1988 during their physical education, driver's education, or health science class. Not all of the students participated because of scheduling difficulties. The authors delivered the questionnaires to the athletic director before the start of the school day. The athletic director distributed the survey to the teachers, who then administered it to the students. The students were advised only that this was a confidential questionnaire, and they were told by the teacher that no questions were allowed. The students completed the questionnaire during the allotted 40-minute time period, and the authors picked up the completed questionnaires at the end of the school day. The authors of the study had no contact with the students.

RESULTS

Of the 3047 students in the school, 2113 completed the survey. There were 534 in grade 9, 496 in grade 10, 518 in grade 11, and 542 in grade 12. There were 1028 males and 1085 females. Ninety-four (4.4%) students admitted using anabolic steroids (Table 1). Broken down by sex, 67 (6.5%) of 1028 males took steroids, as did 27 (2.5%) of 1085 females.

When the students were asked if they participated in sports, 1473 responded that they did participate and 636 said they did not (not all students answered every question). When the use of anabolic steroids was analyzed with respect to sports participation and nonparticipation, the data revealed that of 1436 students who participated in sports, 79 (5.5%) used steroids (Table 2). Of the 79 athlete steroid users, 55 were male and 24 were female. Six hundred thirty-six students did not participate in sports, and 15 (2.4%) in this group were steroid users. Of the 15 nonathletic steroid users. 12 were male and 3 were female.

Of the 1436 students who participated in sports, 833 were male and 603 were female. Fifty-five male athletes (6.6%) were steroid users, and 24 female athletes (3.9%) were steroid users (Table 3).

that with which this confistaff University 1.	Grade level - freshman sophomore junior senior Male Female High school sports in which you have participated or will participate this year	14. 15. 16.	Has a member of the coaching staff or any faculty every suggested that you use an anabolic steroid to help you in high school athletics? yes no Has anyone other than your high school faculty ever suggested that you use anabolic steroids? yes no Are you aware of any medical risks associated with the use of anabolic steroids? yes no (If you answered "no" please skip to question #17) What are the medical and health risks of anabolic steroids? Would you consider using anabolic steroids, if you thought they would help you in high school athletic program? yes no Would you consider using anabolic steroids to help you in a sport done outside of school? yes no
	badminton		outside of select. Tes in
	baseball basketball	19.	Does anyone you know use anabolic steroids? yes no
	field hockey	20-	Have you ever used anabolic steroids? yesno
	football		If "yes" where did you obtain the steroids?
	gymnastics		coach doctor friend other
	soccer		
	softball	21.	Do you plan to participate in college athletics?
	swimming		yes no unsure
	track	22.	Are you hoping to obtain an athletic scholarship to college?
	volleyball		yes no
	tennis track volleyball wrestling		
	other	23.	Would you take anabolic steroids if you thought it would help you obtain a
			college athletic scholarship?
4.	High school athletics in which you have participated in previous years:		yes no unsure
	: none	24	Have you ever considered a career as a professional athlete?
		24.	yes no unsure
5.	Are you a member of a varsity team? yes no		yes _ no _ under _
	If "yes" which one(s):	25.	Are you aware of the use of anabolic steroids by professional athletes?
	a section of the section of achoris yes		yes no
6.	Do you participate in any sports outside of school? yes no		
	If "yes" which one(s)?	26.	Do you feel that in some cases it might be appropriate for professional
7	Do you participate in any type of training program for sports outside of		athletes to use steroids to build up strength or speed? yes no
/.	achoel 2 was no		
	school? yes no	27.	Do you believe that steroids really do build up muscle strength or help
0	Have you ever attended a sports camp or any summer sports program not		with speed? yes no
0.	affiliated with your high school? yes no	20	n bull a block to small be seen for you to obtain stagetide if you
	attitiated attit logi might school. Tes	28.	Do you believe that it would be easy for you to obtain steroids if you
a	Have you had a routine check up from a physician during the past year?		wanted them? yes no unsure
	yesno	29	Where do you get your information about anabolic steroids?
		23.	Friends Television "Muscle" Magazines Doctors Other
10.	Have you ever had an injury requiring medical attention because of		
	participation in high school athletics? yes no	THIS	ENDS THE QUESTIONNAIRE. AFTER RECHECKING TO MAKE SURE YOU HAVE ANSWERED
		ALL	THE QUESTIONS, PLEASE HAND IT TO THE PERSON ADMINISTERING THE SURVEY FOR
11.	Has a physician or any medical personnel ever prescribed any medicine for sports-related injuries? yes no		S CLASS. AGAIN - THANK YOU.
1,200	and the state of t		
12.	Has a member of the school's coaching staff or any faculty ever given you		
	any medication for a sports injury? yes no		

Fig 1.—Survey of general knowledge about steroids.

When the 94 steroid users were analyzed by grade in high school and sex, the data revealed that 23 (13 males and 10 females) were in grade 9, 24 (18 males and 6 females) were in grade 10, 24 (18 males and 6 females) were in grade 11, and 23 (18 males and 5 females) were in grade 12 (Fig 2).

The 1436 students who participated in sports played a total of 2614 sports, 1.8 sports per student. The 79 athlete steroid users participated in a total of 176 sports, 2.2 sports per student. Table 4 shows the relationship between the number of participants in a single sport and the incidence of steroid use by the athletes competing in that sport. The three sports with the lowest incidence of steroid use were track (13 users [4.0%], 327 participants), swimming (18 users [5.0%], 358 participants), and soccer (12 users [5.3%], 227 participants). The sports with the highest incidence of steroid use were football (20 users [9.3%], 214 participants), wrestling (16 users [12.2%], 131 participants), and other (22 users [13.3%], 165 participants).

When the students were asked if a coach or faculty member ever suggested the use of steroids to help them in sports, 43 (2.0%) said yes and 2045 (96.8%) said no. When asked if anyone else suggested the use of steroids, 101 students (4.8%) responded yes and 1989 (94.1%) responded no. Nine hundred twenty-two students (43.6%) said they were aware of the medical risks associated with the use of steroids, and 1159

Table 1.—Overall Incidence of Steroid Use

Total Steroid Users, No. No. (%)

All students 2113 94 (4.4)
Males 1028 67 (6.5)
Females 1085 27 (2.5)

(54.9%) were not. When asked if they knew anyone who used steroids, 332 (15.7%) said yes and 1744 (82.5%) said no. Two hundred eighteen students (10.3%) said they would use steroids to help in high school sports, while 1778 (84.1%) would not. Five hundred fifty-four students (26.2%) were hoping to obtain a college athletic scholarship, while 1499 (70.9%) were not. When asked if they would take steroids to help them obtain a college athletic scholarship, 199 (9.4%) responded yes, 1603 (75.9%) responded no, and 286 (13.5%) were unsure.

The students were asked if they believed steroids helped increase strength or speed; 1145 (54.2%) responded ves and 861 (40.7%) responded no. When asked about their information source on steroids, 734 (34.7%) said they received information from television, 578 (27.4%) from friends, 127 (6.0%) from "muscle" magazines, 101 (4.8%) from physicians, and 310 (14.7%) from others. When asked if it would be easy to obtain steroids, 732 (34.6%) said yes, 439 (23.2%) said no, and 875 (39.6%) were unsure. When the 94 steroid users were asked about their source, 23 said they obtained steroids from coaches, 31 from physicians, 43 from friends, and 24 from others (Fig 3).

COMMENT

This study documents, for the first time, to our knowledge, the use of anabolic steroids among high school students. Based on our findings, 4.4% of the students have used anabolic steroids, with female use at 2.5% and male use at 6.6%. There are few studies available for comparison, but the 6.6% use of steroids by males in our study is strikingly close to the 6.64% use of 12th-grade males recently reported, but less than the 11.1% use in 11th-grade males in a recent publication. ²⁷

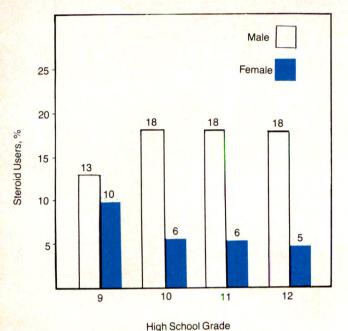
We expected the use of steroids to be higher in athletes than nonathletes, and the results supported that contention; 5.5% of athletes used anabolic steroids. while 2.4% of nonathletes were users. Compared with college and professional athletes, 5.5% may seem out of proportion. The National Collegiate Athletic Association tested 546 football players at 25 volunteer institutions in an offseason anabolic steroid testing program, and 18 athletes (3.3%) tested positive (NCAA News, August 17, 1988). The National Football League tested 1600 players for anabolic steroids before the 1987 season, and 6% were found to be users (New York Times, October 26, 1988, sports section, p 39). Caution must be used, however, in the comparison of the data from these studies with our study for the following reasons: (1) The ages of the athletes are different. (2) Our results are from a questionnaire, while the other studies reported results from actual testing. (3) The designers of the other studies do not tell us how much advance notice the collegiate and professional athletes had prior to the testing. This factor may account for the seemingly low amount of steroid use among more highly skilled athletes. It seems somewhat hard to believe that high school athletes would have a higher incidence of steroid use than college football players and just slightly less than professional football players.

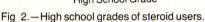
We were surprised to find that 15 students (2.4%) who did not participate in sports used anabolic steroids. The survey did not ask about the reasons for using the drug, so we can only speculate that the reason was to improve appearance. Appearance was the second-most-common reason for steroid use, behind improving athletic performance, as reported in a recent study.³⁰

We thought the results would show a higher incidence of steroid use in the upper grades than the younger grades.

Table 2.—Characteristics of Steroid Users							
	Sports Participants	Nonparticipants					
Total No. of students	1436	636					
Steroid users, No. (%)	79 (5.5)	15 (2.4)					
Male	55	12					
Female	24	3					

Table 3.—Inci	dence of Athlete	At the lateral state of the la
	Total No.	Steroid Users, No. (%)
Male athletes	833	55 (6.6)
Female athletes	603	24 (3.9)





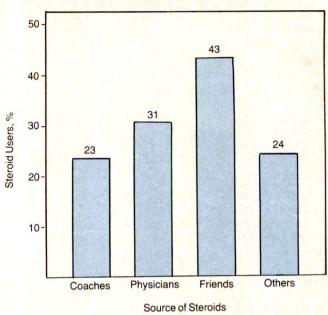


Fig 3.-Sources of steroids.

Sport	Participants	Steroid Users, No. (%		
Track	327	13 (4.0)		
Swimming	358	18 (5.0)		
Soccer	227	12 (5.3)		
Basketball	291	16 (5.5)		
Tennis	105	6 (5.7)		
Volleyball	152	9 (5.9)		
Gymnastics	135	8 (5.9)		
Softball	135	8 (5.9)		
Field hockey	95	6 (6.3)		
Badminton	153	12 (7.8)		
Baseball	126	10 (7.9)		
Football	214	20 (9.3)		
Wrestling	131	16 (12.2)		
Other	165	22 (13.3)		

However, the study showed an almost equal distribution of drug use in students irrespective of their grade level. In fact, the highest number of female steroid users was in grade 9 (n=10), twice as many as grade 12 (n=5). Although the use of anabolic steroids by a high school student is disturbing, it seems particularly distressing that the youngest students are active users of these drugs. This points out the need to question junior high school–aged students about steroid use and to realize

that educational programs about the dangers of steroids must be presented in the junior high schools as well as the high schools.

The main reason for steroid use by athletes has been to increase strength and, thus, athletic performance, although the data to substantiate that fact are not conclusive. 12,14 The fact that football (9.3%) and wrestling (12.2%), two sports in which strength is thought to be a major asset, have the highest incidence of steroid use is no surprise. "Oth-

er" has the highest incidence of steroid use (13.3%). It is possible that many steroid users in this category are weightlifters or bodybuilders. Badminton is thought to be a "finesse" sport, one in which quickness, agility, and hand-eye coordination are important. However, 7.8% of badminton players are steroid users. This suggests that young athletes in any sport may feel that steroids will help them become better athletes.

Physicians and others in the health care field need to be aware that they are at the bottom of the list as an information source about anabolic steroids. Television was mentioned as the most frequent source of information, followed by friends, "others," "muscle magazines," and, lastly, physicians. In this situation, those who should be most aware of anabolic steroids are providing the least amount of information to these high school students.

Thus, the sources revealed by anabolic steroid users do not seem surprising. The most common source was friends, which indicates that users obtained steroids illegally. The next-most-common source was physicians. This situation certainly raises interesting questions. Until recently it was legal in the state of Illinois for physicians to prescribe anabolic steroids for any reason. This situation raised the fol-

lowing questions: Were these physicians unaware of the side effects? Did they sincerely believe they were helping their patients? Was it ethical for physicians to prescribe anabolic steroids for improvement of athletic performances or simply to improve appearances? Although the law in Illinois now prohibits physicians to prescribe anabolic steroids except for certain specific medical conditions, the medical profession in other states will need to address these questions in the very near future. "Others" were the next-mostcommon source, followed closely by coaches. It seems distressing that coaches would provide steroids to their athletes, but with such a great emphasis on winning rather than participation, perhaps this finding is not surprising.

Several questions were designed to elicit the perceptions students have about anabolic steroids. Over half of the students (54.2%) believed that anabolic steroids would help improve their strength and/or speed. This is not surprising in view of all the recent publicity about steroids in all aspects of the media. The medical community remains somewhat ambivalent about whether

steroids improve strength or speed, as evidenced by the most recent position paper of the American College of Sports Medicine, which states "The gains in muscular strength through high-intensity exercise and proper diet can be increased by the use of anabolic-androgenic steroids in some individuals." It is doubtful that many of the users fully understand the concept of high-intensity exercise and even less likely that they have proper diets.

Even with an overall incidence of 4.4% steroid use, 10.3% of students stated that they would use steroids to help them in high school sports, and about the same number (9.4%) said they would take steroids if they would help in obtaining a college athletic scholarship. When these two statements are combined with the fact that 15.7% of the students knew someone who took steroids, it seems reasonable that the actual use of steroids may be somewhat higher than reported by the students. In a survey such as this, it is not always possible to objectively validate the results. However, every effort was made to ensure the confidentiality of each student's response, and there is no apparent reason to think that the students underreported the use of steroids. The questionnaire method of collecting data is consistent with published reports. ^{30,33} Other studies have shown that self-report methods about drug use in this age group have been reliable and valid. ^{34,35}

In summary, this study documents the use of anabolic steroids among the high school-aged population. Based on our survey, 4.4% of all students and 5.5% of athletes have used anabolic steroids. Inferential evidence from our study seems to suggest that students may have underreported use of the drug. If the incidence anabolic steroid use in this group is applicable to the national population, about 700 000 high school students use anabolic steroids. If this is an accurate estimate, we have another serious, as yet unappreciated, drug problem in our adolescents.

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We thank Ann Devitt and Samir Miari for their help in data analysis.

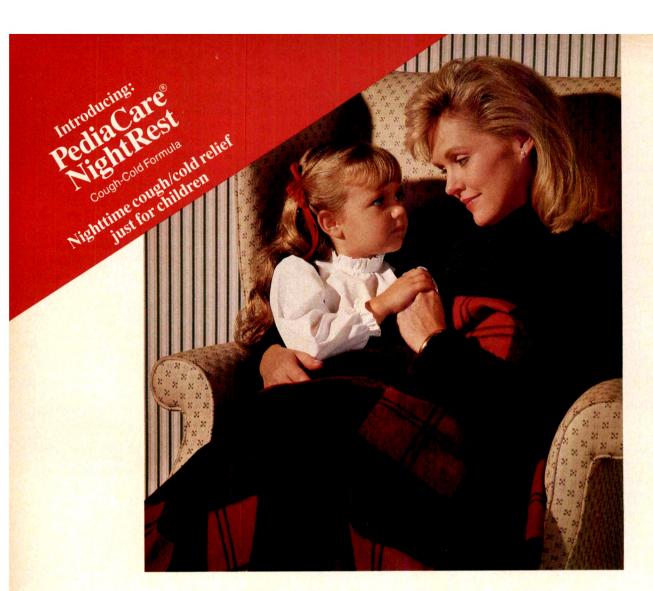
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Articles

Wood-Burning Stoves and Lower Respiratory Tract Infection in American Indian Children

Karen Morris, MD; Marcia Morganlander, MD; John L. Coulehan, MD, MPH; Sheila Gahagen, MD; Vincent C. Arena, PhD

· Some studies suggest that home use of wood-burning stoves is an independent risk factor for lower respiratory tract infection in young children. To test this hypothesis in a population with a high prevalence of wood-burning stove use, we studied Navajo children with diagnosed pneumonia or bronchiolitis. We matched each case (≤24 months of age) with a child of identical sex and age who was seen for well-child care or a minor health problem, and we interviewed an adult caretaker about family history and environmental exposures. Analyzing 58 case-control pairs, we found that home wood-burning stove use, recent respiratory illness exposure, family history of asthma, dirt floors, and lack of running water in the home increased the risk of lower respiratory tract infection. On multiple logistic regression analysis, however, only wood-burning stove use and respiratory illness exposure were independently associated with higher risk.

(AJDC. 1990;144:105-108)

Lower respiratory tract infections (LRTIs) are a major cause of morbidity and mortality in young children. The incidence of all LRTIs approaches 20% to 25% for the first 2 years of life and decreases steadily with age. In Great Britain, 5% to 10% of infant deaths are due to LRTI, mostly acute bronchiolitis and pneumonia. Bronchiolitis alone accounts for 11% of LRTI cases during the first year of life, decreasing to 6% by age 2 years. Although the case fatality rate of bronchiolitis is less than 1%, bronchiolitis and viral pneumonia at an early age are

associated with later pulmonary function abnormalities, additional LRTIs, asthma, and other respiratory symptoms. ⁵⁹ These findings suggest a link between childhood LRTI and chronic lung disease and emphasize the importance of prevention of bronchiolitis and viral pneumonia.

Several inherited and environmental factors are associated with increased risk of LRTI. A family history of asthma, 9-11 respiratory allergy, 9 and chronic cough12 are possible genetic risks. Prematurity and mechanical ventilation increase the infantile bronchiolitis rate.13 Congenital or structural abnormalities also increase the incidence of LRTI.5 Numerous environmental factors have been implicated. Parental smoking, especially during the first year of life, is a consistently demonstrated risk factor. 10-12,14-17 Other, less-well-established risks are gas stove use, 16,18 crowded living conditions, 10,11,19 high number of siblings, 10 school-age siblings, 10,11 low socioeconomic status, 19,20 air pollution, 21 non-breast-feeding,22 and wood-burning stove (WBS) exposure. 23,24

An unpublished preliminary study done at the Indian Health Service Tuba City (Ariz) Hospital in 1987 showed a possible relationship between WBS exposure and an increased incidence of bronchiolitis and pneumonia. The Navajo and Hopi people living on their northeast Arizona reservations are unusual in the United States because many live in traditional housing without electricity, gas, or running water and use a WBS as the sole source of heat. The prevalence of cigarette smoking is also low on the reservation, decreasing the influence of one of the strongly associated risks for LRTI. In this matched case-control study we tested the hypothesis that home use of a WBS is associated with an increased risk of LRTI in young children.

SUBJECTS AND METHODS Selection of Patients

The US Public Health Service Hospital at Tuba City is the principal source of both inpatient and outpatient medical care for about 20 000 Navajo and Hopi people who live in the Tuba City service unit (about 4000 square miles) on the Navajo Reservation. The hospital also provides inpatient care for an additional 15 000 Navajo who live in the adjacent Kayenta service unit, which has its own ambulatory health center. The closest sources of private or non-Public Health Service health care are over 70 miles from Tuba City in Flagstaff or Page, Ariz.

Children 24 months of age or younger who presented to the Tuba City Hospital outpatient clinic or emergency department were identified as cases, controls, or exclusions. Case children were those with a diagnosis of bronchiolitis or pneumonia. To be included, a case of pneumonia required the following: (1) fever and respiratory distress as evidenced by retractions, grunting, flaring, or paroxysmal breathing; (2) clinical evidence of pulmonary infiltrate, such as rales, decreased breath sounds, or dullness in response to percussion; and (3) infiltrates present on chest roentgenogram. To be included. a case of bronchiolitis required the following: (1) fever, (2) respiratory rate over 45/min, (3) wheezes on clinical examination, and (4) respiratory distress. Control children were drawn from those who presented to the outpatient clinic for well-child care. had no acute infectious disease (eg. upper respiratory tract infection, otitis media, gastroenteritis, or conjunctivitis), and had no history (by interview and chart review) of LRTI. Acute dermatologic conditions were not excluded, and 6 controls did have Candida diaper rash, impetigo, or dermatitis. Patients who by chart review had a history of asthma, prematurity, ventilator dependency, or congenital heart disease were ineligible to be either cases or controls.

One control patient was matched by age and sex with each case. Cases and controls were considered suitable matches if they were the same age (within 0.5 months). Over an 8-week period from January 4 to February 27, 1988, 81 cases and 69 controls met our

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inclusion and exclusion criteria. From these we were able to construct 58 age- and sexmatched pairs. The 23 unmatched cases were similar in age and sex distribution to matched cases, but no appropriate matches were available in the pool of 69 potential controls.

Collection of Data

The adult caretaker presenting with the child was interviewed. This was nearly always a parent or grandparent. Using a structured questionnaire, one of two interviewers determined the primary source of energy for heat and cooking in each household. Other environmental factors reported included recent (ie, within 2 weeks in the home) respiratory illness exposures, number of persons in the household, number of rooms, other home characteristics (eg, dirt floor, running water), use of humidification methods, presence or absence of cigarette smoke in the home, and presence or absence of pets. Translators were utilized when necessary.

Statistical Analysis

All analyses performed on the data set preserved the matched study design. For each factor, a fourfold table was constructed summarizing the number of pairs in which both the case and control were exposed (designated as A), case exposed and control not exposed (B), case not exposed and control exposed (C), and neither case nor control exposed (D). The odds ratio is B/C and is the maximum likelihood estimate, based solely on the discordant pairs. This ratio serves as an estimate of the relative risk in the matched analyses.25 McNemar's test26 is an asymptotic test of significance as to whether the odds ratio is equal to 1 (indicating no associated risk). To evaluate the effect of several covariates simultaneously, the conditional logistic regression model was used. Estimation of the modes was based on the maximum likelihood methods described by Breslow and Day²⁷ and was performed using the microcomputer software package EGRET.²⁸ Factors were entered into the regression model in a stepwise fashion, and their respective $\boldsymbol{\beta}$ coefficients were tested to see if they significantly differed from 0 (indicating no association). Odds ratios may be computed by exponentiating the coefficients of the resultant model and serve as estimates of the relative risk for that particular factor while adjusting for other covariates in the model. Confidence intervals are formulated by exponentiating: $\beta \pm 1.96$ (SE).

RESULTS

Fifty-eight age- and sex-matched pairs of children were analyzed. Ages ranged from 2 weeks to 24 months. The

prevalence of environmental risk factors is demonstrated in Table 1. Fortynine case families (84%) and 33 control families (57%) had a WBS in their home. In 21 pairs (36%), the case member utilized a WBS as a primary heating source while the control member did not; in only 5 pairs (9%) did the control member rely on a WBS for heat while the case member did not (odds ratio, 4.2; P=.0012). Coal as an adjunctive fuel did not influence the risk of LRTI as long as a WES was also employed.

The mothers of significantly more case than control children reported recent respiratory illness exposures (odds ratio, 3.7; P = .002), primarily acute illnesses of other children in the home or extended family. Case children also more frequently had a family history of asthma (odds ratio, 3.3; P = .046), 14 children (24%) vs 7 children (12%). Cigarette smoking was infrequent in these Navajo families, with only 3 cases (5%) and 8 controls (14%) having cigarette smoke in the home (odds ratio, 0.4; not significant). Interestingly, the use of humidifiers, vaporizers, or pans of boiling water to humidify air in the home was not associated with protection from LRTI. Neither of the indexes of crowding (number of people in household or number of rooms) was associated with a greater risk of respiratory illness. Although only a few families had dirt floors in their homes, children in these families were more likely to be ill

(P=.016), and, alternatively, there was a trend for those who had running water in the home to be protected against LRTI (odds ratio, 0.5; P=.061).

Multiple Logistic Regression

The following factors were evaluated in the conditional logistic model: WBS. family history of asthma, recent respiratory illness exposure, and presence of running water in the household. These covariates were found to be statistically significant or approaching significance (P < .07) in the univariate analyses and contained substantial numbers of discordant pairs in the data. As shown in Table 2, the final model only contained main effects of WBS and recent exposure. Tests of interaction between the different combinations of covariates were performed, and the results were nonsignificant. Thus, only the presence of a WBS in the home and recent exposure to other ill children were independently associated with the current episode of LRTI.

COMMENT

We investigated risk factors for acute LRTI in young American Indian children and found that those living in homes with a WBS have a higher risk of clinical bronchiolitis and pneumonia than age- and sex-matched controls. These results are consistent with those of Honicky et al^{22,23} and Kossove. ²⁴ Such increased risk may be due to indoor air

Factor	Cases, No. (%)	Controls, No. (%)	Odds Ratio*	P*
Wood-burning stove for heat	49 (84)	33 (57)	4.2	.001
Hurridification†	45 (78)	44 (76)	1.1	.500
Recent respiratory illness exposure	28 (48)	12 (21)	3.7	.002
Cigarettes in home	3 (5)	8 (14)	0.4	.113
Pets in home	44 (76)	39 (67)	1.5	.212
Family history of asthma	14 (24)	7 (12)	3.3	.046
>7 people in home	19 (33)	12 (22)	1.8	.143
1-Room home	14 (24)	12 (21)	1.2	.416
Runring water	34 (59)	43 (74)	0.5	.061
Dirt floor	7 (12)	1 (2)		.016

*Odds ratios and P values are based on case-control matched-pair analysis (McNemar's test). †Humidifier, vaporizer, water pans.

Table 2.—Conditional Logistic Model								
Term	Coefficient	SE	Odds Ratio	95% Confidence Interval	P			
Wood-burning stove Respiratory	1.58	0.53	4.85	1.69-12.91	.003			
illness exposure	1.44	0.50	4.23	1.58-11.30	.004			

pollution, heating variability, and/or other factors and may be influenced by variables such as the type and availability of fuel, ventilation, and insulation and WBS location in the home. Studies of outdoor air pollution and LRTI have had conflicting results.2,8,20 Differences between outdoor and indoor air pollution may relate to the quantity of pollutants and/or duration of exposure, an especially pertinent factor in young children confined to the house. Coal use in the stove did not vary between study and control groups. The other factor associated with LRTI in our logistic regression model was recent respiratory illness in other siblings, a well-known risk factor for bronchiolitis.

The associations with dirt floors and lack of running water in the home, significant in bivariate analyses, could be a reflection of socioeconomic status. Low socioeconomic status has been associated with respiratory symptoms. 19,20 However, other socioeconomic indicators, such as crowding or number of rooms in the house, did not appear to discriminate between groups in our population. Other studies have failed to find a correlation between LRTI and socioeconomic indicators, such as mother's education, number of bathrooms, and formal education achieved by the head of household. 8,11,15,23 Lack of running water and dirt floors may be associated with an increased risk of infection and, thus, are not independent of recent infectious disease exposure.

A family history of asthma has been associated with childhood LRTI in some studies and not in others. ^{10,12,24} Sims et al¹⁴ concluded that environmental rather than inherited factors are the most likely link between severe respiratory illness in infancy or chronic or recurrent respiratory illness in adult life. Others found that LRTI before age 2 years and family history of respiratory allergy are

equivalent risks. In this study, family history of asthma did not contribute independently to risk, suggesting that such a history may simply potentiate or modify the occurrence of LRTI when environmental factors such as a WBS are also present.

Surprisingly, neither cigarette smoking nor humidification were related to occurrence of LRTI. Since ambient cigarette smoke is acknowledged to cause respiratory symptoms in young children, the American Academy of Pediatrics discourages smoking around children less than 2 years of age. 17 The lack of correlation in our study likely reflects the extraordinarily low rate of smoking in this population, with only 9% of homes having a smoker in residence. Honicky et al noted no relationship between humidifiers and respiratory symptoms in children. Humidification lowers air particulate matter and reduces dry air respiratory tract irritation. However, the impact of home humidifying techniques in this desert environment is uncertain.

One possible source of bias in our study is our selection of controls from clinic attenders, who may not be representative of all Navajo and Hopi children. Except for those with minor dermatologic complaints, we limited our controls to those being seen for routine well-child care. Well-child clinic attenders may represent a more mobile or higher socioeconomic group of Navajo and Hopis, perhaps decreasing the likelihood that their families relied on a WBS in the home. However, Public Health Service data indicate that over 90% of children born at Tuba City Hospital complete their routine immunizations, suggesting that the well-child population is, in fact, representative.

It is also possible that our control population was contaminated by children who did indeed have a previous episode of LRTI. Since some medical records were incomplete and since many children had also been seen at other clinic sites, we relied heavily on the mother's memory to exclude previous LRTI. If, however, some children with previous LRTI were included in the control group, it would constitute a conservative bias, tending to minimize the differences between study groups.

Finally, interviewing by nonblinded observers may have biased the study. The use of a highly structured questionnaire with a multiple-choice format and standard conventions for accepting data (eg, entering the caretaker's first response to a question) were designed to decrease the potential for this bias but could not eliminate it entirely.

Further studies will require more specific assessment of the cause of lower respiratory tract symptoms to discriminate among infectious, allergic, and irritant phenomena. Likewise, additional studies should employ more direct environmental data; for example, direct analyses of indoor pollutants, smoke content, house and stove ventilation, and specific substances used as fuel. Leaderer et al²⁸ suggested methods to measure indoor pollutants via monitoring data and daily-use diaries.

In conclusion, our study demonstrates that southwestern American Indian children living in homes heated with a WBS have an increased risk of LRTI independent of recent exposure to others with respiratory illness in the home. This may be an important modifiable risk factor in such traditional rural communities.

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The Inaccuracy of Axillary Temperatures Measured With an Electronic Thermometer

John M. Ogren, MD, FAAP

• Temperatures were measured using an electronic thermometer in an emergency department to determine the relationship between oral or rectal and axillary measurements. A total of 164 data pairs were obtained-95 in afebrile children. and 69 in febrile children. The correlation coefficient was .74 for oral-axillary pairs, and .70 for rectal-axillary pairs. The mean difference between oral and axillary temperatures was 1.17°C ± 0.72°C, and between rectal and axillary temperatures was 1.81°C±0.97°C. Using 37.4°C (≥2 SDs) axillary as the upper limit of normal. the sensitivity, specificity, and positive and negative predictive values were calculated for detecting a fever. The sensitiv-Ity was 46%; specificity, 99%; positive predictive value, 97%; and negative predictive value, 72% for combined oralaxillary and rectal-axillary data. It was concluded that axillary temperatures are not sensitive enough to determine a fever when measured with an electronic thermometer. Electronic thermometers should be used to determine oral or rectal temperatures; axillary temperatures may be misleading and should be abandoned in the outpatient setting.

(AJDC, 1990;144:109-111)

The use of electronic thermometers is gaining acceptance in the home (Consumer Report. January 1988:56) and outpatient¹ and inpatient hospital settings.¹² The reasons include ease of use, accuracy of the reading,³ and rapidity of obtaining a reading (Consumer Report. January 1988:56). Like glass thermometers, there is the possibility of spreading infections especially when obtaining rectal temperatures.

The concern of spreading infection, especially when the thermometer is used rectally, has been eliminated by using disposable sheaths or by taking axillary temperature measurements.¹ Axillary measurements have been advocated for uncooperative children as well as for those children and parents who view rectal measurements as threatening.

While the utility of axillary temperatures in neonates is accepted, the use of axillary temperatures to screen for fever in an outpatient setting is controversial (*Consumer Report.* January 1988:56). Electronic thermometers may not be properly designed to obtain accurate axillary temperatures. ³

For axillary temperature measurements to be useful they should have few false-negative factors (ie, high sensitivity) so that fewer children with a fever are missed. In addition, to minimize unnecessary investigations few false-positive factors (ie, high specificity) are preferable.

Predictive values are useful in allowing one to sense the validity of a screening test. A positive predictive value states how often a patient with a positive test result has the condition while a negative predictive value indicates how often a patient with a negative result is free of the condition. The Pearson Product-Moment Correlation Coefficient is frequently cited as establishing the usefulness of a test. The Pearson coefficient is an indicator of the linear relationship between two variables with r equal to 1 being a perfect relationship. Previous studies⁶⁸ utilizing electronic thermometers to measure axillary temperatures have failed to state the sensitivity, specificity, and predictive values for their measurements. Correlation coefficients for rectal-axillary measurements range from .627 to .906 depending on the method of measuring the axillary temperature.

This study was designed to look at the

relationship between axillary vs oral or rectal temperatures using a digital electronic thermometer in an emergency department setting and assess the usefulness of this method in screening for fever.

PATIENTS AND METHODS

All children 14 years old or less presenting to the emergency department between July 18, 1988, and September 5, 1988, were eligible for participation in the study. As part of their routine assessment nurses took measurements of vital signs including pulse, respiration, and temperature. A Diatek 600 digital thermometer (Diatek Inc, San Diego, Calif) was used for all study patients. The Diatek 600 thermometer is designed to give an audible signal ("beep") when a stable reading is obtained. Axillary temperatures were taken by holding the probe next to the skin under an arm until the reading was stable (approximately 30 seconds) as indicated by a beep. If the child was old enough to cooperate, an oral temperature was taken holding the probe under the tongue. If the child was unable to cooperate for an oral temperature, a rectal temperature was obtained by placing the probe into the rectum. The probe was held in place until the temperature was stable as indicated by a beep.

On a special sheet the nursing staff recorded date, time the data were collected, chart number, age, sex, diagnosis, and temperatures that were taken. Both temperatures obtained were recorded on the emergency department report for the treating physician to use. After the data collection was finished, the thermometer was checked against a calibrated thermistor.

RESULTS

A total of 159 children were initially entered in the study. Three children were excluded because no axillary temperature was taken. In addition, 3 children had all three measurements obtained, namely, axillary, oral, and rectal. Five children had more than one data set obtained either because of multiple visits to the emergency depart-

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ment or multiple measurements during a visit. A total of 164 data sets were obtained - 103 oral-axillary and 61 rectal-axillary sets. There were 82 boys and 74 girls; 54 patients were less than 3 years old. There were two patients less than 3 years old who were cooperative enough for oral temperatures. Fever was defined as a rectal temperature of greater than or equal to 38°C or an oral temperature of greater than or equal to 37.8°C.1 There were 71 oral-axillary and 24 rectal-axillary data sets that were afebrile. These were combined to determine a mean afebrile axillary temperature.

The mean afebrile axillary temperature was 36.1°C ($\pm 0.67^{\circ}\text{C}$), and 2 SDs above the mean was greater than or equal to 37.4°C . Axillary temperatures greater than or equal to 37.4°C were considered positive for predicting a fever (fever), while axillary temperatures less than 37.4°C were considered negative for predicting a fever (no fever).

Using the above definitions, sensitivity, specificity, positive predictive value of a "fever" axillary temperature for being febrile, and negative predictive value of a "no fever" axillary temperature for being afebrile were calculated. The sensitivity was 46% (32/69), specificity was 99% (94/95), positive predictive value was 97% (32/33), and negative predictive value was 72% (94/131) for combined data. There was no difference if the data were calculated for oral-axillary and rectal-axillary separately (Table 1).

To improve the sensitivity of the screening process (Table 2), other values of axillary temperatures were used as screening levels. These corresponded to mean axillary temperature (36.1°C) and 1 SD from the mean (36.8°C). Sensitivity, specificity, and positive and negative predictive values were calculated at these levels.

Those children with "no fever" axillary temperatures but documented fevers (false-negative) included 12 who had temperatures greater than 38.9° C (Table 3). The Pearson coefficient was calculated for oral-axillary (r=.74) and rectal-axillary (r=.70) pairs. For febrile patients the Pearson coefficient was .77 for oral-axillary and .68 for rectal-axillary data. The difference between oral or rectal and axillary

Table 1.—Sensitivity, Specificity, and Predictive Values for Detecting Fever Using Axillary Measurement*

	Axillary "Fever"	Axillary "No Fever"	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Cral (n = 103) Afebrile	1	70	15/32	70/71	15/16	70/87
Febrile	15	17	47%	99%	94%	80%
Rectal (n = 61) Afebrile	0	24	17/37	24/24	17/17	24/44
Febrile	17	20	46%	100%	100%	54%
All data (n = 164) Afebrile	1	94	32/69	94/95	32/33	94/131
Febrile	32	37	46%	99%	- 99%	72%

^{*}Axillary fever, greater than or equal to 37.4°C; oral fever, greater than or equal to 37.8°C; rectal fever, greater than or equal to 38.0°F.

Table 2.—The Accuracy of Three Different Axillary Temperatures for Predicting Fever*

Axillary Temperature	Sensitivity, %	Specificity, %	Positive Predictive Values, %	Negative Predictive Values, %
37°C	46	99	97	72
37℃	67	87	79	78
36°C	87	43	57	82

^{*}Oral fever, greater than or equal to 37.8°C; rectal fever, greater than or equal to 38.0°C.

Age, y	Diagnosis	Axillary, °C	Rectal or Oral, °C
3 mo	URI	37.2	39.4r
21 mo	Otitis media	37.2	39.1r
22 mo	Otitis media	37.4	39.7r
2 y	Otitis media	37	39.7r
2 y	Otitis media	37.2	39.0r
2 y	FWLS	37.3	39.9r
2 y, 6 mo	FWLS	36.9	39.3r
2 y, 11 mo	Pharyngitis	36.1	40.20
3 у	FWLS	36.8	38.9r
3 у	Pharyngitis	37.0r	38.9г
5 y	UTI	36.6	39.10
6 y	UTI	37.0r	39.10

^{*}URI indicates upper respiratory tract infection; FWLS, fever without localizing signs; UTI, urinary tract infection.

measurements was averaged. Oral temperatures were $1.17^{\circ}\text{C} \pm 0.72^{\circ}\text{C}$ higher than axillary temperatures; rectal temperatures were $1.8^{\circ}\text{C} \pm 0.97^{\circ}\text{C}$ higher.

COMMENT

The presence or absence of a fever is frequently used by physicians and families for deciding when to institute antipyretic treatment, seek medical care, or do extensive evaluation. The reliability of the thermometer and the site of measurement become important in making this determination. Shann and MacKenzie, in their study of 75 patients using an electronic thermometer, found a correlation of .9 between axillary and rectal temperatures. They left the thermometer in place for 1 minute, which is not the way most are designed or marketed for use. This may account for their obtaining a higher correlation coefficient than was obtained in our study.

Martyn et al⁹ studied the relationships between axillary, rectal, and forehead measurements. They used an electronic thermometer for axillary and rectal temperatures. No comment was made on how long the probe was held in the axilla. Their patient population did not include children vounger than 1 year, nor did they include any febrile patients (rectal temperature >38.3°C). They found a "better" relationship for rectal-forehead temperatures than for rectal-axillary temperatures. Their conclusion was that the optimal method of measuring body temperature was an electronic thermometer used rectally. Barrus⁷ studied a group of hospitalized children aged 2 to 6 years. Although no details are given of how long the axillary measurements were taken, inclusion criteria included the fact that the patient was at bed rest for at least 30 minutes prior to measurement and was quiet while the measurement was taken. Using an electronic thermometer the mean difference for rectal-axillary temperatures was 0.42°C, and no specificity or sensitivity was reported. Kresch⁵ studied the relationship between rectal, oral, and axillary temperatures in an outpatient setting using glass thermometers. Using an axillary temperature of 37.3°C they found a sen-

sitivity of 33.3%, specificity of 97.7%, and positive predictive value of 78%. The conclusion was that axillary temperatures measured with a glass thermometer were not accurate in detecting a fever.

The results of the present study indicated a slightly better sensitivity of 46%; however, more than 50% of all children with fevers were missed. This includes 12 children with temperatures greater than 38.9°C, 6 of whom were less than 2 years old. Our use of 37.4°C for axillary fever was based on our own afebrile group's distribution. Various studies have used different values 5-7,9 of axillary temperatures, so a constant standard is not applicable. Using lower axillary temperatures increases the sensitivity but sacrifices the specificity and positive predictive value. Fevers would not be missed, but many unnecessary evaluations would result. There is a good amount of confidence that a fever is present if the recorded axillary temperature was more than or equal to 37.4°C; however, the correlation is so weak that the height of the fever is not known.

The present study points out the problem with axillary temperatures, namely, the high incidence of false-negative results. Although axillary tem-

peratures might be improved using longer times in the axilla, this would defeat the purpose of using digital thermometers. Digital thermometers are accurate for measuring rectal and oral temperatures; however, axillary temperature measurements are not accurate and should be abandoned.

I thank the Nursing Department of the Memorial Hospital Emergency Department for their diligence in data collection, Thomas Hadley, MD, for his editorial comments, and Vicki Elliott for secretarial assistance.

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Comparison Study of Intraosseous, Central Intravenous, and Peripheral Intravenous Infusions of Emergency Drugs

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 Intraosseous infusion of emergency drugs is a lifesaving alternative to intravenous administration when intravenous access cannot be rapidly established. We studied the comparative pharmacokinetics of the following six emergency drugs and solutions: epinephrine hydrochloride, 0.01 mg/kg; sodium bicarbonate, 1 mEg/kg; calcium chloride, 10 mg/kg; hydroxyethyl starch, 10 mL/kg; 50% dextrose in water, 250 mg/kg; and lidocaine hydrochloride, 1 mg/kg. Studies were conducted in normotensive, anesthetized dogs, with three animals studied with each of the drugs or solutions and each animal being treated with all three routes of administration (central intravenous, peripheral intravenous, and intraosseous) in randomized sequence. The effects of epinephrine were also assessed in a shock model. The intraosseous route of administration was comparable with the central and peripheral intravenous routes for all of the emergency drugs and solutions studied, with equivalent magnitudes of peak effect or drug level and equal or longer durations of action. Time to placement of the intraosseous needle varied from 15 seconds to 5 minutes, with a mean of 60 seconds. Time to placement of the needle varies with the skill and experience of the individual. With experience, all individuals could place the intraosseous needle in 60 seconds or less. The intraosseous route is comparable in effect to the central and peripheral intravenous routes of drug administration for epinephrine, sodium bicarbonate, hydroxyethyl starch, calcium chloride, 50% dextrose in water, and lidocaine and is a clinically feasible alternative when intravenous access will be critically delayed.

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 \prod he technique of intraosseous infusion is a lifesaving alternative when intravenous access is impossible or will be

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critically delayed. Despite the skill of many physicians, it is occasionally difficult to establish intravenous access, especially in children. This problem is compounded in the infant or child in a state of shock or cardiac arrest. In these situations, volume resuscitation is frequently needed and requires direct access to the circulatory system. If peripheral venopuncture cannot be accomplished, central venous catheterization or venous cutdown are options, but both require experience, take time, and are fraught with potential complications. A study from a pediatric emergency department revealed that in 24% (16/66) of cardiac arrest situations, venous access required more than 10 minutes, and in 6% of the cardic arrests, intravenous access was never obtained.

Intraosseous infusion is a technique for access to the circulation. It is actually an intravenous infusion through intramedullary blood vessels within the bone marrow that are held open by a rigid, noncollapsible bony wall. Unlike peripheral veins, the intramedullary blood vessels do not collapse in shock.2

To be of the greatest use as an emergency alternative to intravenous access, intraosseous infusion of drugs and solutions should be comparable in effect to intravenous infusion. This study was undertaken to compare the pharmacokinetics of emergency drugs and solutions administered by the intraosseous, central intravenous, and peripheral intravenous routes.

MATERIALS AND METHODS

This study was approved by the Animal Care and Research Projects Committee of the Cleveland (Ohio) Clinic Foundation.

Twenty-one dogs, weighing 18.4 to 26.8 kg, were studied with a 14-gauge bone marrow needle in the distal femur: a 16-gauge, 2-in intravenous catheter in the femoral vein; and a 16-gauge, 2-in intravenous catheter in a peripheral forepaw vein. Distance of each catheter from the right atrium was estimated by surface measurements in centimeters. The animals were maintained in an anesthetized state with pentobarbital sodium. The drugs and solutions administered by the intraosseous, central intravenous (femoral vein), and peripheral intravenous routes were as follows: epinephrine hydrochloride, 0.01 mg/kg; sodium bicarbonate, 1 mEq/kg; calcium chloride, 10 mg/kg; lidocaine hydrochloride, 1 mg/kg; 6% hydroxyethyl starch in normal saline, 10 mL/kg; and 50% dextrose in water, 0.25 g/kg. Three dogs were studied with each drug or solution administered by each of the three routes in a randomized sequence. The drug effect or level was allowed to return to baseline for at least 30 minutes before the drug was administered by an alternate route. Epinephrine effect was assessed by change in blood pressure, sodium bicarbonate by a change in pH, and end-tidal carbon dioxide concentration, calcium chloride, by ionized calcium concentrations, lidocaine by plasma concentrations, hydroxyethyl starch by colloid osmotic pressure, and 50% dextrose in water by blood glucose concentrations. Drugs were injected as a bolus followed by 5 mL of normal saline to clear the catheter. Studies of the effect of epinephrine in a shock model were also performed, in which the animal was acutely bled to 50% of its total blood volume (assuming a blood volume of 80 mL/kg), and the effects of epinephrine on blood pressure when administered by all three routes were compared.

Statistical analysis was by paired t test, analysis of variance, and Duncan's Multiple Range Test. Significance was determined by a P<.05.

The time required for a nurse, resident, and staff physician to place a bone marrow needle without prior experience and after five successful attempts was also analyzed.

RESULTS

Figure 1 shows the effects on systolic and diastolic blood pressure of epinephrine hydrochloride (0.01 mg/kg) injected as a bolus followed by 5 mL of normal saline by the central intravenous, peripheral intravenous, and intraosseous routes. The curves were indistinguishable, and no statistically significant dif-

Reprint requests to Pediatric Intensive Care, The Cleveland Clinic Foundation, One Clinic Center, 9500 Euclid Ave, Cleveland, OH 44195-5086 (Dr Orlowski).

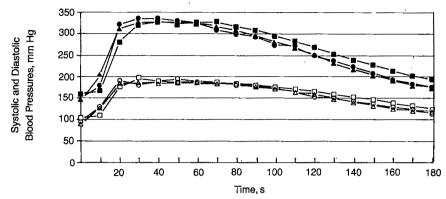


Fig 1.—The effects of systolic (solid markers) and diastolic (open markers) blood pressure of 0.01 mg/kg of epinephrine hydrochloride injected as a bolus by the central intravenous (circles), intraosseous (squares), and peripheral intravenous (triangles) routes, followed by a 5-mL normal saline flush. No statistically significant difference was noted in the time to onset of action, time to peak effect, magnitude of peak effect, or duration of effect between the three routes of administration.

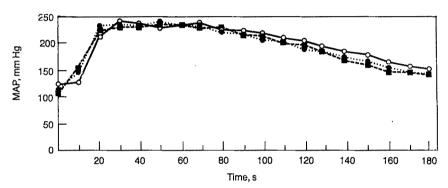


Fig 2.—The effect on mean arterial pressure (MAP) of 0.01 mg/kg of epinephrine hydrochloride administered by the central intravenous (closed circles), intraosseous (open circles), and peripheral intravenous (solid squares) routes in initially normotensive dogs. The results were statistically identical between the three routes.

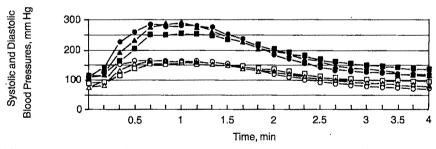


Fig 3.—Results of administering 0.01 mg/kg of epinephrine hydrochloride by the central intravenous (circles), intraosseous (squares), and peripheral intravenous (triangles) routes to animals acutely bled to 50% of their blood volume. No statistically significant differences were noted in the effects on systolic (solid markers) or diastolic (open markers) blood pressures between the three routes of administration.

ference was noted in time to onset of action, time to peak effect, height of peak effect, or duration of effect between the three routes of administration. Figure 2 shows the effects on mean arterial pressure of epinephrine injected by the central intravenous, intraosseous, and peripheral intravenous routes in normotensive dogs.

Figures 3 and 4 compare the effects of

epinephrine administered by the three routes in a shock model, in which the animal had been bled to 50% of its blood volume and allowed to stabilize hemodynamically before the study. Again, the results were statistically the same, with no difference in effects between the three routes of central intravenous, intraosseous, and peripheral intravenous injection.

Figure 5 demonstrates the changes in end-tidal carbon dioxide percentage after the administration of 1 mEq/kg of sodium bicarbonate by the central intravenous, intraosseous, and peripheral intravenous routes. The intraosseous route was slower to reach peak effect (P<.05), but the duration of effect on end-tidal carbon dioxide concentration after intraosseous injection was longer (P < .05). The intraosseous route was intermediate between the peripheral and central intravenous routes in terms of height of peak effect and was an acceptable intermediate alternative between central and peripheral intravenous routes when comparing peak effect and duration of effect. Injection times were different between the three routes. Central intravenous injections averaged 8.8 seconds, peripheral intravenous injections averaged 11.1 seconds, and intraosseous injections averaged 13.5 seconds.

Figure 6 shows the change in ionized calcium levels after the bolus injection of 10 mg/kg of calcium chloride by the central intravenous, intraosseous, and peripheral intravenous routes. No statistically significant difference was noted in the results between the three routes.

Figure 7 shows the change in colloid osmotic pressure after the infusion of 10 mL/kg of 6% hydroxyethyl starch in normal saline into the central intravenous, intraosseous, and peripheral intravenous catheters. The infusion into the intraosseous catheter took significantly longer (20 minutes vs 8 minutes for central intravenous infusion) when allowed to infuse by gravity. When the hydroxyethyl starch was administered by an infusion pump so that infusion times were all the same, the intraosseous route took longer to reach peak effect (P<.05) but also had a significantly greater magnitude of change in colloid osmotic pressure (P < .05).

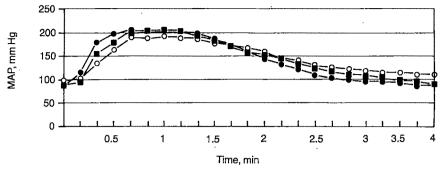


Fig 4.—The effects on mean arterial pressure (MAP) of 0.01 mg/kg of epinephrine hydrochloride administered to dogs in shock from acute hemorrhage to 50% of their initial blood volume. The results were statistically identical. Solid circles indicate central intravenous infusion; open circles, intraosseous infusion; and solid squares, peripheral intravenous infusion.

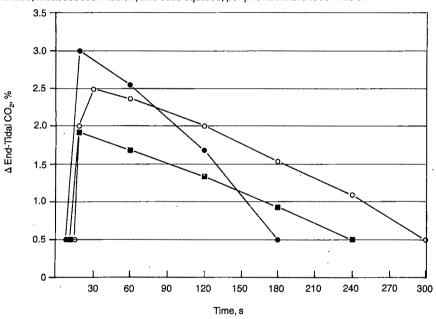


Fig 5.—Changes in end-tidal carbon dioxide concentration after the administration of 1 mEq/kg of sodium bicarbonate by the central intravenous (solid circles), intraosseous (open circles), and peripheral intravenous (solid squares) routes. The intraosseous route was slower to reach peak level (P<.05), but the duration of effect on end-tidal carbon dioxide was longer (P<.05). Injection times were significantly different between the three routes, with central intravenous infusions averaging 8.8 seconds, peripheral intravenous infusions averaging 11.1 seconds, and intraosseous infusions averaging 13.5 seconds. The intraosseous route was intermediately between the peripheral and central intravenous routes in terms of height and peak level of end-tidal carbon dioxide.

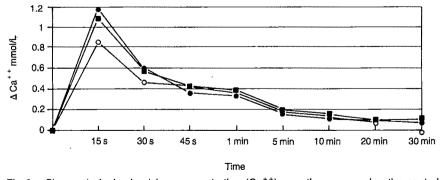


Fig 6.—Change in ionized calcium concentration (Ca⁺⁺) over time, comparing the central intravenous (solid circles), intraosseous (open circles), and peripheral intravenous (solid squares) administration of 10 mg/kg of calcium chloride. No statistically significant difference was noted between the three routes.

Figure 8 is a graph of the change in blood glucose levels over time after the administration of 250 mg/kg of 50% dextrose in water by the central intravenous, intraosseous, and peripheral intravenous routes. The central intravenous and intraosseous routes were statistically similar. The peripheral intravenous route was less (P<.05) in magnitude of peak blood glucose concentration.

Figure 9 shows the different pharmacokinetic curves for the bolus injection of 1 mg/kg of lidocaine hydrochloride by the central intravenous, intraosseous, and peripheral intravenous routes of administration. The central intravenous injection had a more rapid onset of action (P<.05) but a statistically similar magnitude time of peak drug level and duration of measured drug level to the intraosseous injection. The peripheral intravenous injection had a lower magnitude of peak drug level (P<.05).

The time required to place a bone marrow needle successfully, including aspirating the marrow and injecting the drug, was assessed with a critical care nurse, a resident, and a critical care staff physician. Inexperienced insertions required from 2 to 10 minutes. After experience with at least five insertions into the distal femur of the dog, all persons involved could perform successful intraosseous needle placement in less than 60 seconds. All insertions were observed and critiqued by the senior author (J.P.O.), who has experience with intraosseous needle placement and infusions.

COMMENT

The technique of intraosseous infusion is an important emergency alternative for access to the circulation when intravenous access cannot be established or will be critically delayed. It has important advantages over the other emergency alternative of endotracheal drug administration, which is limited to four drugs: epinephrine, atropine, lidocaine, and naloxone hydrochloride. Volume replacement therapy for shock cannot be accomplished by the endotracheal route. Peripheral and even central veins may collapse in shock or cardiac arrest, making access to the venous circulation extremely difficult. Infants and small children may further tax the skills of the physician in establishing intravenous access because of the small size of their veins. Unlike peripheral veins, intramedullary blood vessels in the bone marrow do not collapse in shock because they are held open by a rigid, noncollapsible bony wall.²

Despite clinical application of the technique of intraosseous infusion since the 1940s, 3,4 only a few reports have compared the effectiveness of intraosseous infusion with central or peripheral intravenous infusion. Tocantins et al³ compared the effects of 0.1 mg of epinephrine hydrochloride administered by the central intravenous (femoral vein), intraosseous (tibial bone marrow), and intramuscular routes with a control of saline injected intratibially in a normotensive dog. The blood pressure response to epinephrine by the central intravenous and intraosseous routes was similar in intensity and duration, whereas intramuscular epinephrine and saline control intratibially produced no response. Our results with epinephrine hydrochloride (0.01 mg/kg) injected central intravenously, intraosseously, or peripheral intravenously in both normotensive dogs and dogs in a state of hemorrhagic shock confirm the identical blood pressure responses to epinephrine injection when administered by the intraosseous route compared with the central and peripheral intravenous routes.

Spivey et al⁶ and Thompson et al⁶ compared the effect of sodium bicarbonate administered by the intraosseous and intravenous routes on pH. Spivev et al5 compared the effects of intraosseous. central intravenous, and peripheral intravenous sodium bicarbonate administration on blood pH measured every 2 minutes during cardiopulmonary resuscitation in pigs. They found that the effects of intraosseous (proximal tibia) and central intravenous (superior vena cava) sodium bicarbonate were comparable but were both statistically superior to the effects of peripheral (distal forelimb) intravenous sodium bicarbonate administration and the controls. Thompson et al⁶ compared intravenous (unspecified) with intraosseous (sternum or femur) routes in normotensive dogs using continuous arterial pH monitoring in the femoral artery. They also analyzed injection time and found that

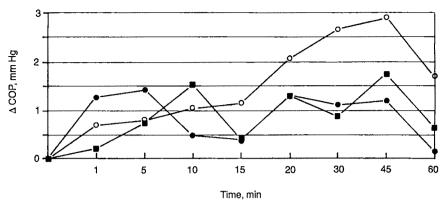


Fig 7.—Changes in colloid osmotic pressure (COP) over time after the administration of 10 mL/kg of 6% hydroxyethyl starch in normal saline by the central intravenous (solid circles), intraosseous (open circles), and peripheral intravenous (solid squares) routes. When the starch was administered by an infusion pump to obtain identical infusion times, the intraosseous route took longer to reach peak level (P<.05) and had a significantly greater magnitude of change in COP and duration of action (P<.05).

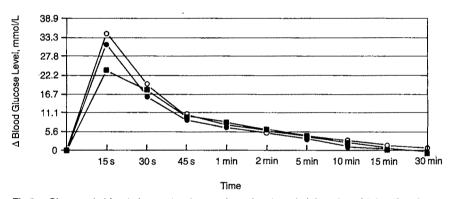


Fig 8.—Changes in blood glucose levels over time after the administration of 0.25 g/kg of 50% dextrose in water by the central intravenous (solid circles), intraosseous (open circles), and peripheral intravenous (solid squares) routes. The central intravenous and intraosseous routes were statistically similar. The peripheral intravenous route had a statistically reduced (P<.05) magnitude of peak glucose level.

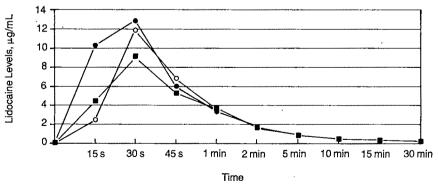


Fig 9.—The effects of 1 mg/kg of lidocaine hydrochloride administered by the central intravenous (solid circles), intraosseous (open circles), and peripheral intravenous (solid squares) routes on plasma lidocaine concentrations. The central intravenous route had a more rapid onset (P<.05), but a statistically similar magnitude and time of peak drug concentration and duration of measured drug level to the intraosseous injection. The peripheral intravenous injection had a statistically lower magnitude of peak drug level (P<.05).

intraosseous injection required 25 seconds compared with 14 seconds for intravenous injection. They found no significant difference in pH changes between the intravenous and intraosseous routes, but the magnitude of their pH changes were dramatically different from the results of Spivey et al, 6 despite using the same sodium bicarbonate dose of 1 mEg/kg. Thompson et al⁶ found a maximum pH change of 0.15 after intravenous injection and a change of 0.12 after intraosseous injection, with no significant difference in time to peak effect between the two routes. Spivey et al5 found a pH change of almost 0.40 to a pH of 7.77 ± 0.09 in the central intravenous group, to 7.71 ± 0.06 in the intraosseous group, and 7.65 ± 0.06 in the peripheral intravenous group. Our pH changes, sampling every 1 minute, were much smaller, with a peak change of 0.08 ± 0.02 in the intraosseous group, 0.06 ± 0.01 in the central intravenous group, and 0.09 ± 0.02 in the peripheral intravenous group. Because of these smaller changes that were difficult to analyze, we decided to follow the effect of sodium bicarbonate by continuous end-tidal carbon dioxide monitoring. Changes in end-tidal carbon dioxide after bicarbonate administration are quite rapid (within seconds), are of sufficient magnitude to easily measure $(500\% \text{ change from } 0.5 \text{ to } 2.5 \pm 0.5)$, and dissipate within minutes. 7,8 Our results demonstrated differences in end-tidal carbon dioxide changes between the three routes in terms of time to peak effect, magnitude of peak effect, and duration of effect. In combination with the pH change data, our results show that intraosseous administration of sodium bicarbonate is an acceptable emergency alternative to the intravenous route. We also found differences in injection time between the three routes. but not of the order of magnitude reported by Thompson et al⁶ probably because of a difference in cannulae size (14-gauge bone marrow needle in our study vs 18-gauge spinal needle in the study by Thompson et al⁶).

Ionized calcium changes after calcium chloride injection by the central intravenous, intraosseous, and peripheral intravenous routes to our knowledge have not been previously reported. Our results demonstrate that the intraosseous route is an acceptable alternative to the intravenous route for the injection of calcium chloride in an emergency.

Likewise, we are unaware of any studies comparing hydroxyethyl starch infusion by the intraosseous, central intravenous, and peripheral intravenous routes. The intraosseous route is effective for the administration of 6% hydroxyethyl starch in normal saline, although the infusion takes considerably longer if administered by gravity infusion. When 6% hydroxyethyl starch is administered by infusion pump at the same rate, the intraosseous route is still slower to reach peak effect but has a higher magnitude of peak effect and more prolonged duration of action. Other authors have described the effectiveness of the intraosseous route for volume resuscitation. Tocantins et al³ demonstrated that they could restore the blood volume of a dog, bled intravenously to 80% of its original blood volume, by reinfusing the blood intraosseously into the sternal blood marrow. Valdes described the volume resuscitation with an average of 4 L of fluid by the intraosseous route of 15 patients requiring fluid administration in an emergency. One patient received 42 L of fluid by the intraosseous route. Morris et al10 resuscitated rabbits bled to 67% of their blood volume using normal saline by the central intravenous (femoral vein) or intraosseous (proximal tibia) route using three times the bled volume of saline. The central intravenous and intraosseous groups were equivalent and statistically different from the control group that was bled but not volume replaced with saline. Neufeld et al" used normal saline (55 mL/min) by the central intravenous, peripheral intravenous, and intraosseous routes to resuscitate piglets bled to a mean arterial pressure of 30 mm Hg. There were no significant differences between the three groups as measured by mean arterial pressure changes, pulmonary capillary wedge pressure, cardiac output, and mixed venous oxygen saturation.

Our results comparing 50% dextrose in water by the central intravenous, intraosseous, and peripheral intravenous routes is the second study of this solution. ¹² Our results demonstrate that the effect of the intraosseous route is equivalent to that of the central intravenous

route and superior to that of the peripheral intravenous route for the solution. As with the other viscous solutions, sodium bicarbonate and hydroxyethyl starch, the bolus administration of the 50% dextrose in water by the intraosseous route is slower and more difficult than intravenous infusion.

Our study of the administration of lidocaine by the central intravenous, intraosseous, and peripheral intravenous routes demonstrated that the peak drug concentration, time to peak drug level, and duration of measured drug level were identical between the central intravenous and intraosseous routes, although the time to onset was slower and more similar to that of the peripheral intravenous injection. The effects of both the central intravenous and intraosseous injections were superior to those of the peripheral intravenous route in peak drug concentration. The duration of measured drug level was the same by all three routes. The only other study of lidocaine was reported in an abstract by Brickman et al,13 who found no statistically significant differences between the effects of intraosseous and central intravenous lidocaine infusions at any interval using a cardiac arrest model in pigs.

Other drugs that have been studied comparatively between intravenous and intraosseous administrations include atropine, diazepam, and phenobarbital. Prete et al14 found that atropine administered by the peripheral intravenous route had a higher peak level and shorter time to peak effect than the intraosseous route, but the intraosseous route had a more prolonged duration of action. Brickman et al15 compared the intraosseous and peripheral intravenous administration of diazepam and phenobarbital in dogs and found them comparable in achieving and maintaining drug levels. Spivey et al16 compared diazepam administered by peripheral intravenous and intraosseous routes for suppressing pentylenetetrazol-induced seizures in pigs. Both routes were statistically similar in effectiveness, and diazepam drug levels were equivalent by the two routes.

Differences in injection or infusion times occurred when comparing the same emergency drug by different routes and when comparing different drugs by the same route. Differences in infusion times of the same drug by different routes were believed to be the result of greater resistance to flow by the intraosseous route with more viscous solutions such as sodium bicarbonate, glucose, and hydroxyethyl starch. The difference in resistance to flow is readily apparent when attempting to inject a viscous solution into the intraosseous needle. For example, sodium bicarbonate could be injected central venously in less than 9 seconds, took more than 11 seconds by the peripheral venous route, and averaged 13.5 seconds by the intraosseous route. Likewise, when allowed to infuse by gravity. hydroxyethyl starch required 20 minutes by the intraosseous route compared with only 8 minutes by the central venous approach. Infusing the drugs or solutions by an infusion pump overcame this resistance and was used in the hydroxyethyl starch studies to ensure that infusion times were equivalent. Differences in infusion times of different drugs by the same route were also seen and reflected differences in volumes of drugs administered as well as differences in resistance to flow. Epinephrine hydrochloride (2 mL) can be injected as a bolus, whereas 25 mL of sodium bicarbonate or 50% dextrose in water will take 10 to 15 seconds and 250 mL of hydroxyethyl starch will take minutes to infuse.

We also assessed the speed with which an intraosseous needle can be inserted, as determined by the ability to aspirate bone marrow and inject saline. Neophytes to bone marrow needle insertion took from 2 to 10 minutes to insert the needle, mainly because of unfamiliarity with how hard one must push and twist to insert the needle into ossified bone. Once they became experienced and overcame their reluctance to push hard, bone marrow needles could be consistently placed successfully in less than 60 seconds and often in less than 30 seconds. Older, reusable needles occasionally bent, requiring use of a new needle. Our results on insertion times compare favorably with other reports in the literature. Brickman et al15 reported intramedullary placement within 15 seconds, and Wagner and McCabe¹⁷ reported an overall success rate of 67.7% using second-year residents without prior training or experience. Success rates for bone marrow and spinal needles were 75%. The average time for placement of the needles in piglets was 27.5 seconds for spinal needles and 11 seconds for bone marrow needles.

A number of sites are available for intraosseous needle insertion in children, including the medial or lateral malleoli, proximal tibia, distal femur. and iliac crest. The sternum has also been used in adults, but is generally not recommended for children. Complications of intraosseous infusion vary from extravasation of fluid into the subcutaneous tissue to osteomyelitis. The cases of osteomyelitis were from the 1940s^{3,4} and were usually in patients in whom infusions had been performed for more than 24 hours. Heinild et al.4 in a review of the literature, found 10 cases of osteomyelitis of a reported 299 infusions and then reported their own series of 1000 infusions with only 5 cases of osteomyelitis. They also reported no abnormalities of the bone marrow in 11 patients examined at autopsy 1 to 14 days after infusion and no cases of clinical or autopsy evidence of fat emboli. Orlowski et al18 have recently reported bone marrow necrosis associated with intraosseous injections of sodium bicarbonate, 50% dextrose in water, epinephrine, and lidocaine and bone marrow and fat emboli in the lungs in all animals and patients studied using specific stains. Despite their findings of bone marrow and fat emboli in 100% of the infusions, there was no evidence of pulmonary abnormalities during the 4 hours of study, which might complicate resuscitation. Nevertheless, the universal finding of bone marrow and fat emboli in the lungs raises questions about the safety of intraosseous infusions in patients with intracardiac right-to-left shunts.

Intraosseous administration of resuscitation drugs and solutions is a very effective alternative to intravenous administration when establishment of an intravenous route will be critically delayed or is impossible. We have demonstrated the equivalency of the intraosseous route to the central intravenous and peripheral intravenous routes for epinephrine, sodium bicarbonate, calcium chloride, 6% hydroxyethyl starch in normal saline, 50% dextrose in water,

and lidocaine. We have also demonstrated that the intraosseous needle can be successfully inserted in less than 60 seconds, which makes it a technically feasible alternative for access to the circulatory system when intravenous access cannot be achieved or will be critically delayed.

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A Profile of Mothers Giving Birth to Infants With Congenital Rubella Syndrome

An Assessment of Risk Factors

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• To formulate strategies for elimination of congenital rubella syndrome, it is important to identify risk factors for delivering an infant affected by it. We analyzed cases of congenital rubella syndrome in infants born from 1970 to 1985 and reported to either one of two independent Centers for Disease Control surveillance systems. Mothers of infants with congenital rubella syndrome identified in both surveillance systems were disproportionately younger than mothers giving birth in the United States. The risk for delivering an infant with congenital rubella syndrome was approximately 2.5 times higher for blacks compared with whites for both reporting systems. A total of 18% of infants with congenital rubella syndrome born since 1979 were Hispanic (national population average, 7%). Both surveillance systems showed that, although primiparous mothers were at highest risk, 39% of women delivering infants affected by congenital rubella syndrome had had at least one previous live birth, suggesting that postpartum immunization could have prevented these congenital rubella syndrome cases. Young, black, and Hispanic primiparous women represent populations at elevated risk for delivering a congenital rubella syndrome-affected infant and should be specifically targeted for immunization.

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The rubella epidemic of 1964-1965 in the United States resulted in approximately 20 000 infants born with congenital rubella syndrome (CRS), more than 11 000 instances of fetal deaths by either miscarriage or therapeutic abortion, an estimated 12.5 million cases of rubella, and an economic impact of \$1.5 billion.

In 1987, only 306 cases of rubella (1.3 cases per 1000000 persons) were reported in the United States, a decline of more than 99% since 1969, the year of rubella vaccine licensure (Fig 1). The current reported total is the lowest since rubella became a nationally notifiable disease in 1966. Recent declines in rates of CRS recorded by the National Congenital Rubella Syndrome Registry (NCRSR) of the Centers for Disease Control (CDC), (Atlanta, Ga) have paralleled the decline in overall rubella incidence and, more specifically, in the incidence in persons 15 years of age or older. Despite a marked reduction in the reported incidence of both CRS and rubella, 64 cases of CRS were reported from 1980 to 1986, each of which has an estimated lifetime cost in excess of \$220 000 in 1982 dollars.1 The actual number of CRS cases that occurred from 1980 to 1986 may have been as high as 640, based on a previously published analysis suggesting that only an estimated 10% of total CRS cases are reported to the NCRSR.2 To formulate strategies for the elimination of indigenous CRS and to target those strategies effectively, it is necessary to identify risk factors associated with delivery of a CRS-affected infant. This report presents such an analysis of data derived

from two independent CRS surveillance systems.

METHODS

We analyzed cases of CRS in children born from 1970 to 1985 and reported to the NCRSR. Because such cases may be subject to reporting bias, we also analyzed information from a second independent CDC surveillance system, the Birth Defects Monitoring Program (BDMP), to determine whether the NCRSR findings could be validated.

The NCRSR is a nationwide passive reporting system initiated in 1969 and maintained in the Division of Immunization at CDC. The system relies on reports from physicians and other health care providers transmitted via local and state health officials. The relatively low completeness (ie, sensitivity) of this reporting system contrasts with the relatively high specificity achieved through detailed clinical and laboratory information provided for each case.

Cases reported to the NCRSR are monitored by year of birth and are classified into six clinical categories, the most specific of which are "confirmed" and "compatible" (Table 1). Since 1984, cases of CRS have further been classified into "indigenous" and "imported" cases. Based on definitions approved by the Council of State and Territorial Epidemiologists, an imported case of CRS is defined as one occurring in a US or non-US citizen whose mother was outside the United States during her presumed exposure to rubella. If the timing of exposure to rubella cannot be determined, then the mother must have been outside the United States throughout the 21 days before conception and the first 20 weeks of her pregnancy. The 20-week period was selected to conform to the maximum known period of risk during gestation that could result in defects in the infant.3-6 We analyzed all confirmed and compatible cases in infants born prior to 1984 and only indigenous cases in infants born since 1984.

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The BDMP is a data set of newborn discharge diagnoses, including CRS, from a nonrandom sample of approximately 25% of US births obtained annually from the hospital discharge data base of the Commission on Professional Hospital Activities (CPHA), and maintained in the Division of Birth Defects and Developmental Disabilities at CDC. The system is highly sensitive in detecting cases of CRS diagnosed during the first few days of life, although only approximately 50% of all cases are detected during this period.^{2,3,7-9} Its specificity is low, however, since many suspected cases of CRS may lack sufficient clinical or laboratory information to confirm the diagnosis. To increase specificity, we obtained discharge summaries on cases of CRS reported to the BDMP and analyzed only confirmed and compatible cases as in the NCRSR system. Because no information on importation is available from the BDMP, all cases were assumed to be indigenous.

We abstracted demographic data accompanying confirmed and compatible cases of CRS reported to each of the two surveillance systems between 1970 and 1985. Rates were calculated using natality data, from the National Center for Health Statistics, for all US births during the study period. As a best estimate of the population at risk, the denominator included mothers of all ages, although during the study period more than 99% of US births were to women less than or equal to 39 years of age. We calculated rates from NCRSR data for race, maternal age, and parity. Because race was the only study variable for which denominator data for CPHA births were available, rate calculations on BDMP data were limited to race.

Rate ratios (relative risks) were calculated as measures of association. To adjust for possible confounding, Mantel-Haenszel rate ratios were calculated using the Rothman and Boice program¹⁰ for cohort data.

RESULTS

There were 413 cases of CRS reported to the NCRSR and 93 reported to the BDMP. A total of 19 (3.8%) of the 506 cases of CRS analyzed were reported to both systems. Since all of the cases reported to BDMP and only 262 of the cases reported to the NCRSR were diagnosed during the neonatal period, 19 (5.4%) of the 355 cases diagnosed at birth were reported to both systems.

Characteristics of CRS cases in each surveillance system are summarized in Table 2. Cases identified by the two systems were similar in distribution by race, gender, whether alive at the time of reporting, and state submitting the

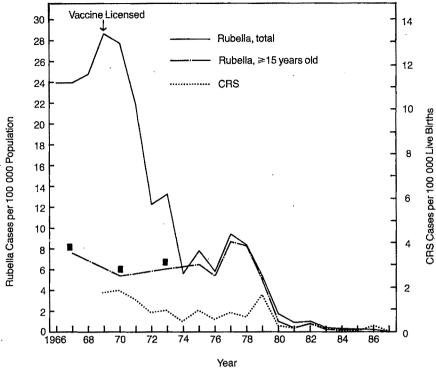


Fig 1.—Incidence rate of reported cases of rubella and congenital rubella syndrome (CRS) in the United States for the period 1966-1987. Confirmed and compatible cases of CRS are shown by year of birth (dotted line); data are provisional due to delayed diagnosis and reporting. Solid boxes indicate average annual US estimate based on data from Illinois, Massachusetts, and New York City for the 3-year periods 1966 to 1968, 1969 to 1971, and 1972 to 1974.

Table 1.—Criteria for Classification of Cases of Congenital Rubella Syndrome (CRS)

- I. CRS Confirmed—Defects present and one or more of the following:
 - a)Rubella virus isolated
 - b)Rubella-specific IgM present
 - c)Rubella hemagglutination-inhibition (HI) titer, or equivalent rubella antibody test result, in the infant persisting above and beyond that expected from passive transfer of maternal antibody (ie, rubella HI titer in the infant that does not fall off at the expected rate of one twofold dilution per month)
- II. CRS Compatible—Laboratory data insufficient for confirmation and any two complications listed in a or one from a and one from b:
 - a)Cataracts or congenital glaucoma (either or both count as one, congenital heart disease, loss of hearing, pigmentary retinopathy
 - b)Purpura, splenomegaly, jaundice, microcephaly, mental retardation, meningoencephalitis, radiolucent bone disease
- III. CRS Possible—Some compatible clinical findings that do not fulfill the criteria for a compatible case
- IV. Congenital Rubella Infection Only—No defects present but laboratory evidence of infection V. Stillbirths—Stillbirths that are thought to be secondary to maternal rubella infection
- VI. Not CRS—One or more of any of the following inconsistent laboratory findings in a child without evidence of an immunodeficiency disease:
 - a)Rubella HI titer (or equivalent antibody test result) absent in a child less than 24 months
 - b)Rubella HI titer absent in mother
 - c)Rubella HI titer decline in an Infant consistent with the normal decline of passively transferred maternal antibody after birth (the expected rate of decline of maternal antibodies is one twofold dilution per month)

report. The five leading states (California, New York, Texas, Illinois, and Michigan) contributing cases of CRS were identical in both systems, although their rank order differed in the two systems. A total of 55% of cases reported to the NCRSR were classified

as "confirmed", compared with only 16% of cases reported to the BDMP, a finding that reflects the lower specificity of the BDMP in the immediate newborn period. Since the BDMP relies on newborn discharge diagnoses, all cases reported to that system were diagnosed

in the first month of life.

Of 27 mothers of infants with CRS reported to the BDMP for whom rubella immunization status at the time of delivery was known, only 1 had the year of rubella immunization recorded. Of 232 such mothers of infants whose cases were reported to the NCRSR, none had received rubella vaccine before deliverv. Within each surveillance system we compared mothers whose rubella immunization status was known to be unvaccinated with those whose immunization status was unknown. There were no differences between the two groups in mother's age, distribution of previous live births, racial distribution of infants, or any of the characteristics listed in Table 2. We therefore combined the two groups within each system for all subsequent analyses and assumed that all were unvaccinated.

Mothers of infants with CRS were disproportionately younger than US mothers giving birth overall, a finding true for both systems. A total of 35% to 40% were 15 to 19 years of age, compared with 16% of all mothers giving birth during the study period (Fig 2). None of the mothers of infants with CRS were older than 39 years of age. Based on the NCRSR cases, the risk of delivering an infant with CRS was 7.1 times greater for mothers 15 to 19 years of age than for those 30 years of age or older (referent). The rate ratio declined with increasing maternal age from 2.7 for mothers 20 to 24 years of age, to 1.9 for those 25 to 29 years of age, and 1.0 for mothers 30 years of age or older (the reference group). Because few births in the United States were to women older than 39 years of age, rates calculated for women 30 to 39 years of age and those for women 30 years of age or older did not differ.

Approximately 25% of infants in both systems were black, compared with the national average for births of black infants which is 16%. The risk of delivering an infant with CRS was approximately 2.5 times higher for blacks compared with whites for both reporting systems (Fig 3). The risk for persons of other races was two times higher based on BDMP data and seven times higher for NCRSR cases. These data were analyzed further in age groups according to the ages of the mothers. Al-

Table 2.—Characteristics of Congenital Rubella Syndrome (CRS) cases*

No. (%)				
NCRSR (n = 413)	BDMP (n = 93)			
04.2 (57)	. (05)			
, ,	59 (65)			
` '	23 (25)			
• •	9 (10)			
35	2,			
215 (52)	46 (50)			
• •	47 (50)			
	47 (00)			

342 (83)	84 (90)			
57 (14)	9 (10)			
14	*** ***			
•				
100 (24)	12 (13)			
49 (12)	6 (6)			
25 (6)	7 (8)			
19 (5)	8 (9)			
15 (4)	13 (14)			
204 (49)	47 (50)			
	15 (16)			
187 (45)	78 (84)			
262 (68)	93 (100)			
· ·	33 (100)			
· · · · · · · · · · · · · · · · · · ·				

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, ,	******			
	216 (57) 104 (28) 53 (15) 35 215 (52) 197 (48) 1 342 (83) 57 (14) 14 100 (24) 49 (12) 25 (6) 19 (5) 15 (4)			

*Data were from the National Congenital Rubella Syndrome Registry (NCRSR) and the Birth Defects Monitoring Program (BDMP). Nineteen cases were reported to both surveillance systems.

though the number of observations in each age group was small, similar trends in risk for blacks and persons of other races were observed within each age stratum. Because no ethnicity data were reported to the NCRSR prior to 1979, some misclassification of white Hispanics in the "other races" category may have contributed to the elevated rate ratio observed. Of 50 infants in the other races category for whom data were available, 35 (70%) had Spanish surnames. Based on more recent NCRSR ethnicity data, 19 (18%) of 105 CRS infants born since 1979 were Hispanic. This finding contrasts with the national average of 7% Hispanics in the population.

Table 3 presents the distribution of

mothers of CRS-affected infants based on age and history of a previous live birth. The proportion of mothers in each age group who had had a previous live birth was similar in the two systems and paralleled the experience of women in the United States. Both surveillance systems indicated that, overall, 39% of women delivering CRS-affected infants had had at least one previous live birth. However, mothers 15 to 19 years of age were less likely to have had a previous live birth (approximately 15% in both systems) than those 30 to 39 years of age (75% to 86% in the two systems). Based on denominator data available for NCRSR cases, primiparous mothers were twice as likely as multiparous mothers to deliver an infant with CRS

(rate ratio, 2.1). When adjusted for the confounding effect of age, the effect of parity, as an independent risk factor, declined (age-adjusted rate ratio, 1.5). Figure 4 shows the rate of CRS per 100 000 live births according to both mother's age and her history of a previous live birth. Young, primiparous mothers were at highest risk; older women who had had a previous live birth had a lower risk. Analysis of each of these three risk factors (age, race, previous live births) in intervals of 5 years showed no trends for the 16-year period.

COMMENT

Based on available information, virtually all of the mothers of infants with CRS were unimmunized, indicating that failure to vaccinate susceptible women, rather than vaccine failure, was responsible for these reported cases of CRS. A limitation of the two data sets was that immunization information was incompletely reported to both surveillance systems. However, the characteristics of the women whose rubella immunization status was unknown did not differ from those who were known to be unvaccinated. Furthermore, when we repeated our analyses including only those mothers of infants with CRS who were known to be unvaccinated at the time of delivery (26 in the BDMP and 232 in the NCRSR), the findings were similar. Since the efficacy of rubella vaccine is estimated to be 90% or greater, and since there has been no evidence of waning vaccine-induced immunity, we believe it likely that the infants with CRS were delivered primarily to unvaccinated mothers.11-13

When rubella vaccine was licensed in 1969, the United States adopted a policy of universal immunization of children; secondary emphasis was placed on vaccinating susceptible adolescents and adults, especially women. Beginning in 1977, efforts were intensified to vaccinate all children as well as susceptible postpubertal women. In spite of the greater use of vaccine in both population groups, a decline in the serosusceptibility rate in postpubertal women below rates found in the prevaccine era (10% to 20%) has been infrequently documented. 14-16 The continued occurrence of rubella in populations of childbearing

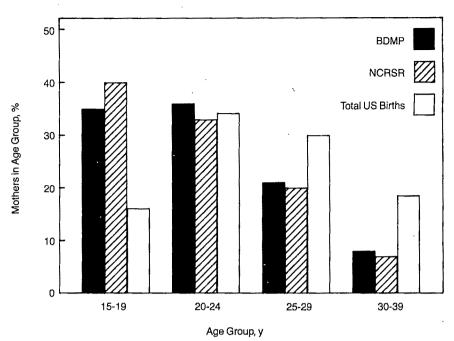


Fig 2.—Age distribution of mothers of infants with congenital rubella syndrome (CRS) is shown from cases reported to the National Congenital Rubella Syndrome Registry (NCRSR) and the Birth Defects Monitoring Program (BDMP) for the period 1970 through 1985.

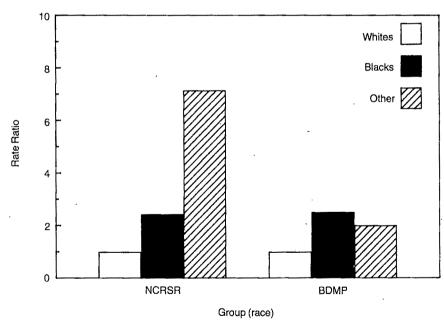


Fig 3.—Rate ratio of congenital rubella syndrome by race of infant is shown based on data from the National Congenital Rubella Syndrome Registry (NCRSR) and the Birth Defects Monitoring Program (BDMP) for the period 1970 through 1985.

age means that potentially preventable cases of CRS will continue to occur until vaccinated cohorts reach the childbearing years. Such concerns led the CDC to announce an initiative in February 1985 to hasten elimination of rubella and CRS by further increasing efforts to target

susceptible populations of childbearing age for vaccination.¹⁷ To be effective, these immunization efforts need to be focused on those groups with the greatest need.

Despite substantial underreporting of cases of CRS and potential concerns

Table 3.—Number of Previous Live Births Among Mothers of Infants With Congenital Rubella Syndrome (CRS) Based on Mother's Age, and Data From the NCRSR* (1979-1985) and BDMP (1970-1985)

	No. (%)						
	,	NCRSR			,	BDMP	
Mother's Age, Y	0	Previous Live Bi ≥1	rths Total	0	Previou	ıs Live Bir ≥1	rths Total
15-19	14	2 (13)	16	27	5	(16)	32
20-24	14	10 (42)	24	20	11	(36)	31
25-29	3	5 (63)	8	6,	13	(68)	19
30+	1	3 (75)	4	1	6	(86)	7
Total	32	20 (39)	52	54	35	(39)	89

^{*}Information on previous live births was not uniformly collected prior to 1979 NCRSR indicates National Congenital Rubella Syndrome Registry; BDMP, Birth Defects Monitoring Program.

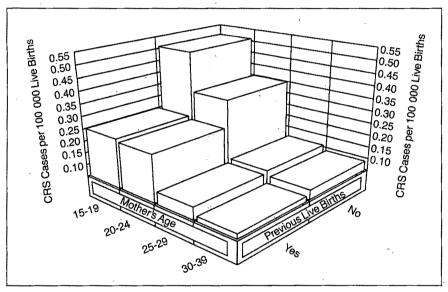


Fig 4.—Rate of congenital rubella syndrome (CRS) per 100 000 live births is plotted against mother's age and history of previous live birth based on data from the National Congenital Rubella Syndrome Registry for the period 1979 through 1985.

about reporting bias in the NCRSR system, the two independent surveillance systems identified similar predictors for delivering an infant with CRS. Our analysis indicates that young, black, or Hispanic primiparous women represent populations at greatest risk of delivering a CRS-affected infant and should be specifically targeted for immunization. Our data are consistent with those in the United Kingdom, which also showed that minority women, specifically immigrants from south Asia, are at high risk for delivering an infant with CRS. 18-20 Of 812 nulliparous Asian women who presented to the Public Health Laboratory Service in three British cities from 1984 to 1985, 86 (10.6%) were susceptible to

rubella, compared with 420 (2.6%) of 16 237 non-Asian women.

As with other adult immunizations, creative multifaceted approaches are necessary to enhance rubella immunization levels in the population of childbearing age. One way to reach susceptible women is to offer rubella vaccine at the time of any encounter with the health care system, with the exception of prenatal visits. This approach should include postpartum as well as postabortion immunization and follow-up immunization of susceptible women identified through preemployment or premarital screening. Based on our data (Table 3), postpartum immunization might have prevented the 39% of cases of CRS in

infants born to mothers who had a previous live birth. This finding is consistent with other studies that indicate that postpartum vaccination may prevent one third to one half of cases of CRS. ²¹ In the study by the British Public Health Laboratory Service during 1984 through 1985, postpartum vaccination reduced rubella susceptibility from 10.6% in nulliparous Asian women to 2.8% in parous Asian women, and from 2.6% to 1.8% in nulliparous and parous non-Asian women, respectively. ²⁰

Because younger mothers of infants with CRS (those 15 to 19 years of age) are less likely to have had a previous pregnancy, there is also a need to identify and immunize susceptible persons in any of a variety of settings—in school, in college, at the workplace, or within the health care system. The family planning clinic setting is an ideal place to offer vaccine and may represent one of the few contacts with the health care provision system of hard-to-reach individuals.

Because of the difficulty in providing rubella vaccine to hard-to-reach persons, every opportunity should be taken to offer vaccine to these individuals. Unfortunately, this frequently does not occur. Following a university-based rubella outbreak in 1985, investigators developed a method for quantitating missed opportunities for rubella vaccination.22 A missed opportunity was defined as a situation in which either recommendations of the Immunization Practices Advisory Committee or state legislation called for rubella vaccination of an individual, but it did not occur. The investigators identified missed opportunities for rubella vaccination at the time of primary or secondary school entry, during the postpartum period, at college matriculation, and prior to employment in a health care setting.

Shortly after rubella vaccine licensure, concern about its teratogenic potential hindered vaccination of women of childbearing age; however, no CRS-like defects have been detected in 212 infants born to susceptible mothers vaccinated with live, attenuated, Wistar rubella virus vaccine (RA 27/3)) during pregnancy.²⁵ After excluding susceptible female patients who might be pregnant and counseling about the advisability to avoid conception for 3 months

following vaccination, practitioners should have no hesitation about vaccinating women of childbearing age against rubella. While pregnancy remains a contraindication to rubella vaccination, routine pregnancy testing prior to vaccination is not recommended. Routine serologic testing prior to rubella immunization also is not recommended.

Concerns about joint reactions associated with the rubella vaccine also have impeded vaccination of susceptible adults. Whereas mild, transient arthritis/arthralgia following vaccination is common, persistent or chronic arthritis/arthropathy is rare. The small risk of

chronic joint symptoms should not interfere with the current strategy of vaccinating susceptible women. ²⁵ Studies of large numbers of vaccinees have found that vaccination of already-immune persons (from either natural disease or vaccination) does not appear to be associated with joint reactions. ^{11,26}

The continued occurrence of imported cases of CRS may mean that the complete elimination of CRS cannot be achieved in the foreseeable future. Between 1984 and 1988, an additional seven reported cases (25% of all cases of CRS reported to CDC) were known to be imported. Every case of CRS should thus be investigated individually

to determine whether it might have been preventable through existing immunization programs.

Rubella control efforts in the United States have been very successful. Elimination of indigenous rubella and congenital rubella is a more difficult task, but appears to be feasible with maintenance of current strategies and targeting of special efforts toward identified high-risk groups. Analyses such as this one, as well as of missed opportunities either in outbreak settings or of healthy persons identified as susceptible by serologic testing, can help focus efforts to fill the remaining gaps in implementing rubella elimination strategies.

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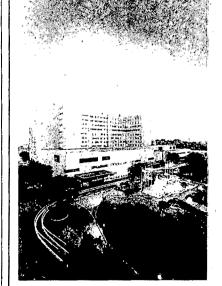
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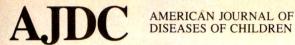
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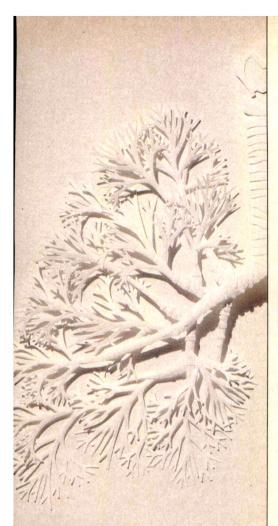
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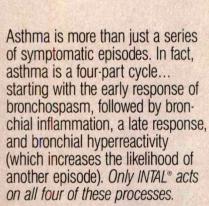
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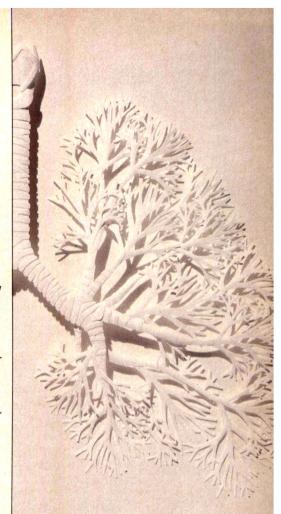


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INDICATIONS AND USAGE: INTAL Inhaler is a prophylactic agent indicated in the management of patients with

CONTRAINDICATIONS: INTAL Inhaler is contraindicated in those patients who have shown hypersensitivity to cromolyn sodium or other components.

WARNINGS: INTAL Inhaler has no role in the treatment of an acute attack of asthma, especially status asthmaticus. Severe anaphylactic reactions can occur after cromolyn sodium administration. The recommended dosage should be decreased in patients with decreased renal or hepatic function. INTAL Inhaler should be discontinued if the patient develops eosinophilic pneumonia (or pulmonary infiltrates with eosinophilia). Because of the propellants in this preparation, it should be used with caution in patients with coronary artery disease or a history of cardiac arrhythmias.

PRECAUTIONS: General: In view of the biliary and renal routes of excretion for cromolyn sodium, consideration should be given to decreasing the dosage or discontinuing the administration of the drug in patients with impaired renal or hepatic function.

Occasionally, patients may experience cough and/or bronchospasm following cromolyn sodium inhalation. At times, patients who develop bronchospasm may not be able to continue administration despite prior bronchodilator administration. Rarely, very severe bronchospasm has been encountered.

Carcinogenesis, Mulagenesis, Impairment of Fertility: Long term studies in mice (12 months intraperitoneal treatment followed by 6 months observation), and rats (18 months subcutaneous treatment) showed on neoplastic effect of cromolyn sodium. No evidence of chromosomal damage or cytotoxicity was obtained in various mulagenesis studies. No evidence of impaired fertility was shown in laboratory animal reproduction studies.

Pregnancy: Pregnancy Category B. Reproduction studies with cromolyn sodium administered parenterally to pregnant mice, rats, and rabbits in doses up to 338 times the human clinical doses produced no evidence of fetal malformations. Adverse fetal effects (increased resorptions and decreased fetal weight) were noted only at the very high parenteral doses that produced maternal toxicity. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Drug Interaction During Pregnancy: Cromolyn sodium and isoproterenol were studied following subcutaneous injections in pregnant mice. Cromolyn sodium alone in doses of 60 to 540 mg/kg (38 to 338 times the human dose) did not cause significant increases in resorptions or major malformations. Isoproterenol alone at a dose of 2.7 mg/kg (90 times the human dose) increased both resorptions and malformations. The addition of cromolyn sodium (338 times the human dose) to isoproterenol (90 times the human dose) appears to have increased the incidence of both resorptions and malformations

Nursing Mothers: It is not known whether this drug is excreted in human milk, therefore, caution should be exercised when INTAL Inhaler is administered to a nursing woman and the attending physician must make a benefit/risk assessment in regard to its use in this situation.

Pediatric Use: Safety and effectiveness in children below the age of 5 years have not been established. For young children unable to utilize the Inhaler, INTAL Nebulizer Solution (cromolyn sodium inhalation, USP) is recommended. Because of the possibility that adverse effects of this drug could become apparent only after many years, a benefit/ risk consideration of the long-term use of INTAL Inhaler is particularly important in pediatric patients.

risk consideration of the long-term use of INTAL Inhaler is particularly important in pediatric patients.

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Adverse reactions which occur infrequently and are associated with administration of the drug are: anaphylaxis, angloedema, dizziness, dysuria and urinary frequency, joint swelling and pain, lacrimation, nausee and headache, rash, swollen parotid gland, urticaria, pulmonary infiltrates with eosinophilia, substernal burning, and myopathy. The following adverse reactions have been reported as rare events and it is unclear whether they are attributable to the drug: anemia, exfoliative dermatitis, hemoptysis, hoarseness, myalpia, nephrosis, periarterific vasculitis, pericarditis, peripheral neuritis, photodermatitis, sneezing, drowsiness, nasal itching, nasal bleeding, nasal burning, serum sickness, stomach ache, polymyositis, vertigo, and liver disease.

OVERDOSAGE: No action other than medical observation should be necessary.

OVERDOSAGE: No action other than medical observation should be necessary.

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DOSAGE AND ADMIRISTRATION: For management of bronchial asthma in adults and children (5 years of age and over) with are able to use the Inhaler, the usual starting dosage is two metered sprays inhaled four times daily at regular intervals.

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Reference: 1. Eigen H, Reid JJ, Dahl R, et al: Evaluation of the addition of cromolyn sodium to bronchodilator maintenance therapy in the long-term management of asthma. J Allergy Clin Immunol 1987:80:612-621

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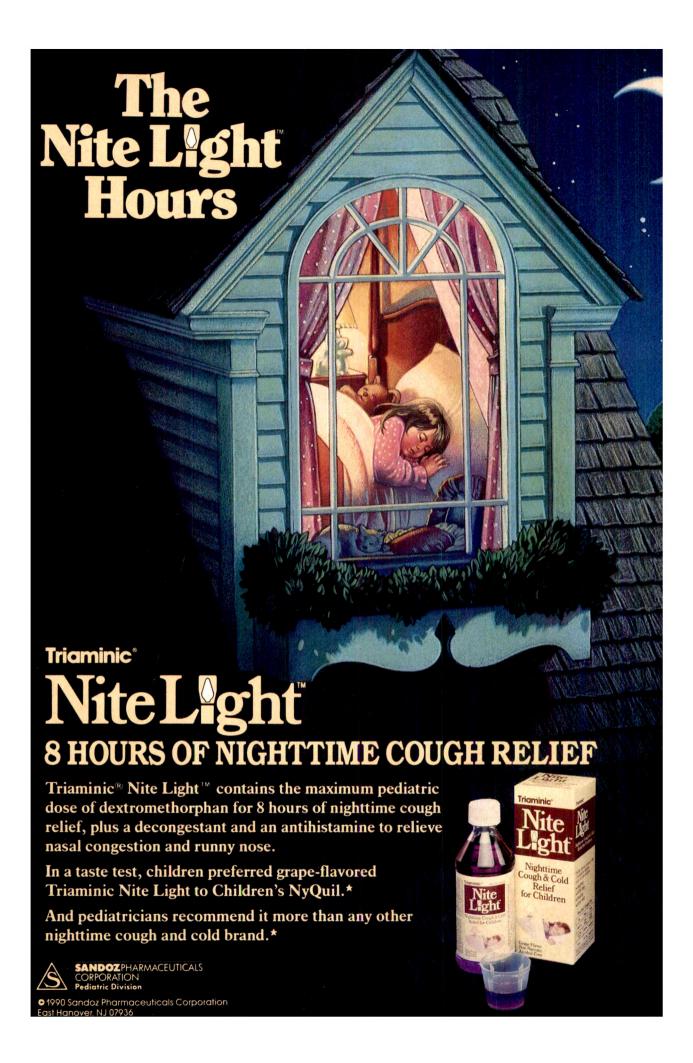
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The Pediatric Forum

This department of AJDC is reserved for comment, criticism, observation, and discussion of "issues of current concern and importance for children's health." The Editor encourages our readers to express themselves on a variety of topics and issues. Further, we encourage the submission of unique and brief clinical and scientific observations that do not fulfill the criteria for original articles.

Rapid Streptococcus Testing and Over-the-Counter Cold Medications

Sir.—I read with interest Taubman and colleagues" excellent article in the January 1989 issue of AJDC. A statement made in the article deserves amplification. The authors state, "One reason for lower specificity may be due to possible interference from over-the-counter cold medications. Such medications have been shown to cause false-positive results with this particular latex test" (Culturette Brand Group A STREP ID).²

In the reference cited, I stated that we had indirect evidence that some false-positive results may be due to the patients' ingestion of certain overthe-counter medications. In these cases, the latex test was positive for group A *Streptococcus*, but in vitro testing showed that β-hemolytic *Streptococcus* reversibly manifested α-hemolysis when exposed to the medication on blood agar plates. Such plates could possibly be misread as "negative for group A *Streptococcus*."

In conclusion, the authors are correct in their statement that false-positive results may be reported; group A *Streptococcus* may be present on the culture plate, but the observation of α -hemolysis may lead one to believe that they are not.

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1. Taubman B, Barroway RP, McGowan KL. The diagnosis of group A, β-hemolytic streptococcal pharyngitis in the office setting. *AJDC*. 1989;143:102-104.

 Uhlik DJ. Rapid diagnosis of streptococcal pharyngitis. Am Clin Products Rev. 1985;9:36-43.

Presentation of False-negative Test Results

Sir.—Taubman et al¹ in the January 1989 issue of AJDC discuss an extremely important issue—use of a rapid latex agglutination test for the detection of group A β-hemolytic streptococcal pharyngitis in an office setting. Their study design demonstrates the importance of comparing a new test with "the gold standard" (ie, a reference laboratory culture) as well as with the customary test (ie, throat cultures incubated and interpreted in the pediatric office). The authors introduce a term, "percent of false-negative results (% FN*)," that they define as follows:

% False Negatives (%FN*) = $\frac{FN}{TN + FN + TP + FP}$

where TN indicates true negatives; TP, true positives; and FP, false positives.

In a situation like this, the risk of undetected group A β -hemolytic streptococcal pharyngitis (ie, the false-negative tests) is usually communicated by the negative predictive value (PV_{neg}) of the test, an established and frequently used term in clinical epidemiology. If the authors wish to refer to the proportion of tests that are inaccurate, the percent of false negatives is more properly defined as false negatives divided only by negative test results rather than by all test results.

Predictive Value, Negative Test

$$(PV_{neg}) = \frac{TN}{TN + FN}$$

% False Negatives (%FN) =
$$\frac{FN}{TN + FN} = 1 - PV_{neg}$$

With this definition, the relationship between %FN and PV_{neg} is clear. Both PV_{neg} and the predictive value of a positive test are influenced by the prevalence of the disease detected by the test. As the prevalence of the disease increases, %FN also increases. With the new definition of %FN rather than %FN*, %FN in the authors' population would increase from 3.0% to 4.6% when compared with the reference laboratory, from 2.3% to 3.3% when compared with the readings of investigator 1, and from 2.8% to 4.1% when compared with the readings of investigator 2.

Introduction of a new term requires a clear definition and should add insight that cannot be gained by use of standard terminology. In this study, PV_{neg} should be used to communicate the risk of missing a case of group A β -hemolytic streptococcal pharyngitis when relying on a rapid latex agglutination test.

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1. Taubman B, Barroway RP, McGowan KL. The diagnosis of group A, β-hemolytic streptococcal pharyngitis in the office setting. *AJDC*. 1989;143:102-104.

Autopsies and Sudden Infant Death Syndrome

Sir.—In their article in the May 1989 issue of AJDC, Chasnoff et al¹ are misled in their belief that an autopsy can rule out lethal trauma in an infant

who is presumptively diagnosed to have died of sudden infant death syndrome (SIDS). It is recognized in forensic pathology that young infants who die of external airway obstruction, accidental or otherwise, may have no pathologic changes on autopsy that indicate lethal injury by suffocation or smothering. In many cases of sudden infant death, death-scene investigation may be the only way to determine why a healthy infant died suddenly and unexpectedly at home.^{2,3}

The data described by Chasnoff and coworkers are based on live infants. However, these infants are unsuitable controls for a study of infants who die of SIDS. The selection of controls in any prospective study of infants who died of SIDS should be restricted to healthy infants of similar ages who died suddenly and unexpectedly of disorders other than SIDS. Examples of suitable controls are infants who die suddenly of smoke inhalation, carbon monoxide poisoning, or other injuries, usually unintentional.

A pathologic relationship between prenatal cocaine abuse and postneonatal sudden infant death is unproved. Finally, the frequent misdiagnosis of lethal injuries as SIDS may be attributed to a lack of trained manpower and financial resources necessary for With death-scene investigation. greater frequency, pediatricians are beginning to appreciate the full extent of the problem concerning the need for on-site investigation of homes in cases of unexplained sudden death and near death in infants.

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1. Chasnoff IJ, Hunt CE, Kletter R, Kaplan D. Prenatal cocaine exposure is associated with respiratory pattern abnormalities. *AJDC*. 1989; 143:583-587.

2. Bass M, Kravath RE, Glass L. Death-scene investigation in sudden infant death. N Engl J Med. 1986;315:100-105.

3. Bass M. The fallacy of the simultaneous sudden infant death syndrome in twins. Am J Forensic Med Pathol. 1989;10:200-205.

In Reply.—We thank Dr Bass for his thoughtful comments. He raises two issues related to the legitimacy of SIDS as a specific clinical entity. As suggested by death scene investigations, he argues that most deaths can be explained by accidental or intended circumstances rather than caused by an underlying pathophysiological abnormality. He also suggests that aberrant home conditions may be an even

more likely cause of (explained) death in infants with prenatal cocaine exposure.

We agree that an autopsy that reveals normal findings may not exclude suffocation as the cause of death. Although our study focused only on living infants and the increased incidence of cardiorespiratory pattern abnormalities following prenatal cocaine exposure,2 there are other studies that do document an increased SIDS rate in infants with prenatal cocaine exposure.2,3 These families may indeed be high risk in numerous ways, but there is no evidence to suggest that as a group the deaths occurring at home are environmentally induced. To the contrary, in fact, there is evidence that prenatal cocaine exposure may pernervous system central turb maturation4 and result in brain-stem dysfunction or maturational delay, such as hypothesized to result in SIDS.3,5

In summary, we agree that death scene investigations may yield a rich database. However, until the causal relationship between sudden infant death and specific home circumstances1 can be verified by a prospective control study, one cannot conclude that such circumstances are any more common in dying infants than in surviving infants. If not more common, one still has the dilemma of determining why infants dying of SIDS are physiologically different from normal infants. Nevertheless, we were not studying the pathophysiology SIDS,2 but rather were evaluating one consequence of prenatal cocaine exposure-an increased occurrence of cardiorespiratory pattern abnormalities. The potential relationship between such abnormalities and risk of SIDS is a crucial question, but one that can only be addressed in future studies.

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- Bass M, Kravath RE, Glass L. Death-scene investigation in sudden infant death. N Engl J Med. 1986;315:100-105.
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- 5. Hunt CE, Brouillette RT. Sudden infant death syndrome: 1987 prospective. *J Pediatr*: 1987;110:669-678.

Respiratory Pattern Abnormalities and Prenatal Cocaine Exposure

Sir.—We recently reported an increased incidence of respiratory pattern abnormalities in infants with prenatal cocaine exposure.¹ A deficient sleep arousal response to asphyxia may be a fundamental abnormality²,³ in infants at risk for sudden infant death syndrome, and at least part of the interrelationship among intrauterine cocaine exposure, subsequent cardiorespiratory pattern abnormalities, and risk for sudden infant death syndrome may be deficient arousal responsiveness.

In the "Comment" section, we suggested a possible relationship among prenatal cocaine exposure, norepinephrine, and the locus coeruleus, the putative center of arousal in the brain stem. Specific references are now available that discuss in full detail the hypothesis originally proposed by Gingras and Weese-Mayer that cocaine-induced alterations in norepinephrine in the locus coeruleus may be secondary to an effect on neural transmitter homeostasis. Furthermore, this hypothesis is now being tested in an animal model5 and in a human model.6

In summary, we are pleased to bring to the readers' attention these new publications hypothesizing a relationship among intrauterine cocaine exposure, brain-stem arousal center abnormalities, and risk for sudden infant death syndrome. Delineation of the perturbations in cardiorespiratory control caused by cocaine may indeed lead investigators to a more thorough and more fundamental understanding of the pathophysiologic characteristics of sudden infant death syndrome.

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Chasnoff IJ, Hunt CE, Kletter R, Kaplan
 Prenatal cocaine exposure is associated with

respiratory pattern abnormalities. AJDC. 1989;

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5. Weese-Mayer DE, Klemka-Walden LM, Gingras JL, Brouillette RT. Effects of in utero cocaine exposure on postnatal respiration in the newborn rabbit. *Pediatr Res.* 1989;25:331A.

 Gingras JL, O'Donnell KJ, Hume RF Jr. Maternal cocaine addiction and fetal behavioral state, I: a human model for the study of sudden infant death syndrome. Med Hypotheses. In press.

Physical Examination for 'Initial Evaluation' of Hypertrophic Pyloric Stenosis

Sir.-I agree with Foley et al1 that ultrasound should not be used for the "initial evaluation" of vomiting in infants. I would go one step further to deplore the use of any roentgenographic or imaging study for the "initial evaluation" of vomiting in infants. The initial evaluation should have been a good history and physical examination that might have eliminated the need for ultrasound or an upper gastrointestinal tract series in most, if not all, of the 37 patients proved by their studies to have hypertrophic pyloric stenosis. Unfortunately, it appears that the knack of palpating a pyloric "olive," which requires evacuation of the stomach and relaxation of the infant's abdominal wall, is not being transmitted from experienced attending physicians to house staff and thus is becoming a lost art. In the absence of a palpable olive, the upper gastrointestinal tract series is the study most likely to yield diagnostic information. However, the most costeffective method for ruling in or out a diagnosis of hypertrophic pyloric stenosis remains a properly conducted physical examination.

> Anthony Shaw, MD Sylmar, Calif

1. Foley LC, Slovis TL, Campbell JB, Strain JD, Harvey LA, Luckey DW. Evaluation of the vomiting infant. *AJDC*. 1989;143:660-661.

Pediatricians Want to Be Called

Sir.—As pediatric gastroenterologists in a referral center, we were surprised by the correspondence of Dr Stickler¹ in the May 1989 issue of *AJDC*, stating

that colleagues should only be telephoned if there is an emergency or information is needed "right this minute." Therefore, we conducted a survey of the 177 physicians who refer patients to us. We asked the physicians whether they wanted to be called at the time of consultation or would rather wait to be notified by letter. Of the 177 physicians polled, 132 (75%) responded. Of those responding, 86% requested a telephone call, 10% preferred not to be called, 2% wanted to be called only for emergencies, and 2% provided miscellaneous answers. We received numerous unsolicited comments, all of which were positive.

We trained in a large center and are cognizant of the ease with which pediatricians can lose patients to an amorphous system. The pediatrician identifies the need for subspeciality consultation and helps the family through an evaluation and necessary follow-up. In instances where the care is complex, involving more than one subspecialist, the pediatrician is in a pivotal position to interpret the many recommendations a family may receive. To perform this function, the pediatrician must have access to subspecialists and, indeed, we believe, the subspecialist has a responsibility to inform the pediatrician of his or her initial evaluation and plan in a timely manner. Since it may take weeks for a letter to reach a referring physician, we developed a system whereby we call the referring pediatrician at the time a patient is first seen. We are always rewarded by the interest and warmth with which our calls are received. We obtain invaluable insights and, at times, alter our initial plan after speaking with the referring physician. In addition to the specific information communicated, we feel a sense of shared experience in providing the best possible care we can to our patients.

Although pediatricians are a harrassed, hard-working lot, when they request a consultation from a subspecialist, they appreciate immediate feedback.

> SUSAN S. BAKER, MD, PHD ROBERT D. BAKER, MD, PHD Department of Pediatrics University of Massachusetts Medical School 55 Lake Ave N Worcester, MA 01655

1. Stickler GB. Telephone etiquette. AJDC. 1989;143:520.

In Reply.—I'd like to make a little statement about the letter by Baker and Baker.

Since the authors studied the problem of making telephone calls to the referring physician, I stand corrected. Obviously, referring physicians want to be called after a consultation has been obtained and find it no intrusion. Perhaps I was thinking about the good old times when we had a mail system that functioned well and when we had physicians who immediately dictated letters to the referring physician. Since there is such a long delay in getting information to the referring physician, a telephone call is obviously the answer.

> GUNNAR B. STICKLER, MD Department of Pediatrics Mayo Clinic Rochester, MN 55905

Ingestion of Aromatic Ammonia 'Smelling Salts' Capsules

Sir.—We recently cared for three children who had bitten into capsules of aromatic ammonia "smelling salts." Each glass capsule, enclosed in a fiber mesh (Fig 1), contained 0.33 mL of a mixture of 18% ammonia and 36% alcohol. The ammonia capsules are usually available as part of home first-aid kits.

Patient Reports.—PATIENT 1.—A 3½-year-old girl bit into a capsule of aromatic ammonia. She denied having swallowed any of its contents. She drank some water afterward without problem, but by the time she was evaluated in the emergency department about 1 hour later, she complained of oral pain on swallowing. Her tongue was red anteriorly with occasional blisters.

PATIENT 2.—A 3-year-old girl presented to the emergency department about 1 hour after she bit into a vial of aromatic ammonia. She was drooling and had erythema and swelling of the lower lip and a superficial denuded burn of the anterior portion of the tongue. She underwent nasopharyngoscopy in the emergency department; this showed no burns of the posterior hypopharynx.

PATIENT 3.—A boy almost 4 years old bit into an ammonia capsule and immediately complained of pain in his mouth. He was offered water afterward and was able to swallow well. He was seen in the emergency department 2 hours later with erythema and swelling of the lower lip and a superficial denuded area of the anterior tongue (Fig 2). He was drooling copiously. No other oropharyngeal burns were seen. He was observed to swallow fluids without difficulty.

Our first two patients were referred for endoscopy because of the presence of oral burns. Both patients underwent esophagoscopy under general anesthesia. Neither pa-



Fig 1.—An aromatic ammonia "smelling salts" capsule.

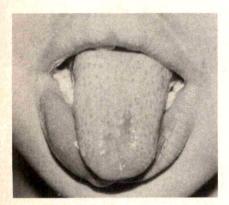


Fig 2.—Patient 3 with denuded tongue epithelium, swollen lower lip, and drool.

tient was found to have esophageal burns. Based on the fact that ammonia is not generally considered to be caustic and that the total amount in each capsule was limited to only 0.33 mL, we predicted that esophageal burns would not likely be present after this form of ammonia ingestion. For this reason we decided to treat our third patient conservatively. The following morning he, too, was asymptomatic.

Comment. - In the first two patients, it was felt that because oral burns were present, the risk of concurrent esophageal injury would be high. While some authors have advocated esophagoscopy in all patients with caustic ingestion regardless of symptoms or signs,1 others have recommended that factors such as the amount of ammonia ingested,2 physicochemical properties,2 and clinical findings (such as stridor, drooling, and vomiting3) need to be taken into consideration before recommending endoscopy. It has been shown that patients with oral burns after ingesting a caustic substance have approximately a 55% chance of having a simultaneous esophageal burn. Conversely, approximately 45% of such patients will not have esophageal burns.4 Our experience supports the findings of Lopez et al,4 who described eight children who had also accidently bitten into ammonia capsules. All of these patients, too, had oropharyngeal burns, and six

had drooling, while three had dysphagia. None of the patients was found to have esophageal burns by endoscopic examination.

We believe that, despite a high concentration of ammonia, these capsules should not be considered to be caustic enough to cause esophageal injury because of the extremely small volume present. We suggest that children who are seen after this unique ingestion should not be subjected to routine endoscopy, thereby sparing them the risk of general anesthesia. Endoscopy should be reserved for only those children with clinical evidence suggestive of upper airway involvement, ie, stridor, dysphagia, or drooling.

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- Gaudreault P, Parent M, McGuigan M, Chicoine L, Lovejoy FH. Predictability of esophageal injury from signs and symptoms: a study of caustic ingestion in 378 children. *Pediatrics*. 1983;71:767-770
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- 4. Lopez GP, Dean BS, Krenzelok EP. Oral exposure to ammonia inhalants: a report of 8 cases. Vet Hum Toxicol. 1988;30:350.

Seizures in the Course of Hepatitis A

Sir.—Convulsions are very rare in the early stages of viral hepatitis. To our knowledge, only four cases have been reported in adults. We present two cases of children who suffered from hepatitis A virus infection with concomitant convulsions.

Patient Reports. - PATIENT 1. - An 8year-old girl was admitted because of generalized convulsive seizure. Eight days prior to admission she started suffering from loss of appetite and vomiting. Two days before hospitalization urinalysis revealed bilirubin. On the day of admission she underwent a first episode of a tonoclonic symmetrical convulsive seizure in all four limbs with rolling of the eyes that lasted 5 minutes. There was no fever at that time, nor was there any history of central nervous system trauma or drug usage. No family history of convulsive disorder could be elicited. On examination, she was slightly jaundiced, and the abdomen was soft, with a mildly tender liver palpated 4 cm below the costal margin, without splenomegaly. Neurologically, she was sleepy but easily awakened, and no signs of hepatic encephalopathy as asteryxis or myoclonus were present. She recovered 6 hours later. Results of the rest of the physical and neurologic examination were normal. Lumbar puncture, done within 15 minutes after the termination of the episode, revealed clear fluid with no cells. The glucose level was 4.2 mmol/L, and the protein level was 0.24 g/L. Cerebrospinal fluid was sterile. Virus culture was negative. The serum bilirubin level was 114 mmol/L, mostly conjugated. Plasma sodium, potassium, glucose, and calcium levels obtained while she was still convulsing were normal. The aspartate aminotransferase level was 350 U/L; alanine aminotransferase, 700 U/L; and alkaline phosphatase, 384 U/L. Results of coagulation studies and a complete blood cell count were within normal limits. Results of a hepatitis B surface antigen test were normal. Immunoglobulin M and IgG antibodies to hepatitis A virus were present. Electroencephalographic examination done on the second day was normal. During 24 months of follow-up she was anicteric, with normal liver function test results. An electroencephalogram was normal, and the convulsion did not recur.

PATIENT 2. - A previously healthy 4-yearold boy underwent a convulsive seizure that lasted 25 minutes and was preceded by vomiting. There was no history of brain trauma, nor did he receive any drugs. On admission he was sleepy and afebrile. His abdomen was soft, and a nontender liver was palpated 2 cm below the costal margin. Neurologically, no signs of hepatic encephalopathy were present, and when awakened he was oriented. Results of the rest of the physical and neurologic examination were normal. Serum glucose and calcium levels were normal. The serum bilirubin level was normal, but the aspartate aminotransferase level was 398 U/L and the alanine aminotransferase level was 400 U/L. Results of a hepatitis B surface antigen test were normal. Immunoglobulin M and IgG antibodies to hepatitis A virus were present. An electroencephalogram on the second day of hospitalization was normal. On reevaluation 16 months later, there had been no convulsions, and a repeated electroencephalogram was normal.

Comment. - Neurologic manifestations in the course of acute viral hepatitis are very rare.1 To our knowledge, convulsive disorder in the early phase of viral hepatitis has been described in four adults.14 Several theories have been proposed to explain the pathogenesis of the neurologic symptoms in acute viral hepatitis. Lucké⁵ postulated that neurologic manifestations were secondary to a disturbed detoxification process by the diseased liver. This is an unlikely explanation because there is no direct correlation between the severity of the hepatic damage and the degree of the neurologic involvement. 1,6 Others have

suggested that a neurotropic virus invades the central nervous system. This is supported by observations in which a neurotropic strain of mice virus produced acute diffuse encephalomyelitis with demyelinization in rats. 7 Nonetheless, as yet, no direct evidence of human hepatitis virus had been detected in the human central nervous system. Activation of a latent central nervous system virus by the hepatitis virus was also proposed but was not proved.6 Immunologic mechanisms were proposed to explain the extrahepatic manifestations. ie, hypersensitivity reaction (Guillain-Barré syndrome and Gianotti-Crosti syndrome [papular acrodermatitis usually associated with hepatitis B infection]).

The pathogenesis of seizures in acute viral hepatitis remains obscure. Mild electroencephalographic changes were found in 5 of 35 children with hepatitis A without convulsions,8 and 44% of patients with hepatitis B had nonfocal. asymmetric mild electroencephalographic changes.9 Our patients had generalized convulsive seizures in the course of hepatitis A virus infection. After excluding other causes for the convulsion, such as metabolic abnormalities, fever, and hepatic encephalopathy, with a long follow-up of at least 1 year, we conclude that the seizures are related to the viral hepatitis. To the best of our knowledge, these are the first cases reported in children and the first cases with proved hepatitis due to type A virus.

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Home Oxygen Administration and Retinopathy of Prematurity: Survey of 1988 Practices

Sir.-Premature infants are subjected to stringent invasive and noninvasive oxygen monitoring in the pursuit of the elusive "safe" path between hypoxic brain damage on the one hand and increased risks of blindness from retinopathy of prematurity (ROP) on the other. For the majority of infants, this period is relatively short. In some infants, however, chronic lung disease leads to such a prolonged oxygen requirement that home oxygen administration is considered. Hudak et al1 have recently reported a growth benefit to 30 infants receiving oxygen at home when their pulse oximetry was kept over 95% saturation. They also stressed avoidance of hyperoxia but did not relate this to the degree of retinal immaturity or ROP present in a particular infant.

The risk for severe ROP appears to be proportional to the degree of retinal immaturity, ie, the amount of avascular retina. It follows from this understanding that when the retina becomes fully vascularized, there should be no further risk of ROP and, therefore, that conservative control of oxygen should logically be continued in any premature infant whose retina is not fully vascularized. On occasion, incompletely regressed ROP has been observed to reactivate in conjunction with a new acute illness at a later age but while the retina is still only partially vascularized (D.L.P., unpublished data, 1983; John T. Flynn, MD, unpublished data, 1983).2 This supports the conclusion that the infant with avascular retina remains at risk for ROP regardless of postconceptional age.

In some nurseries, infants with immature retinas remain hospitalized until they are no longer receiving oxygen or until their retinas mature. This has proven to be the source of considerable local debate regarding the time of discharge and, thus, led to this survey of current practices in the United States for the discharge home of premature infants who still require oxygen. While a majority viewpoint cannot establish a correct answer, the views expressed in this survey reflect the wide range of current practice and lead to specific questions for future investigation.

Methods.—A short, anonymous questionnaire was developed and mailed to the directors of intensive care nurseries at the 603 hospitals listed with the American Medical Association as having either an intensive or intermediate care nursery. With two mailings, 417 responded (69%). Among the responders, 264 (63%) considered themselves a level 3 unit, 147 (35%) a level 2 unit, and 6 (1.4%) responded that they did not have a special care nursery or failed to answer the question.

Results. - Infants requiring oxygen were discharged home at least occasionally by 349 centers (84%), and at 334 of these (96%), ophthalmologic examinations for ROP were performed prior to discharge. Among the 338 hospitals doing ROP examinations (including 4 that did not discharge home infants requiring oxygen), 189 (56%) stated that the ROP results do not alter their discharge plans while 57 (17%) replied that the ROP examination results do influence discharge plans. Eighty-eight (26%) had never encountered the problem of ROP or retinal immaturity at the time of discharge planning for an infant requiring home oxygen administration.

Although only 57 (17%) of the responders stated that the results of the ROP examination influence whether an infant requiring oxygen can be discharged home, 83 centers described the manner in which ophthalmic evaluation might alter discharge plans. This discrepancy in numbers reflected opinions about ROP among those who had "never encountered this problem." Of the 154 centers who described discharge criteria, in 25 (16%), any amount of avascular retina or ROP made the infant ineligible for discharge home while still receiving continuous oxygen. In 58 (38%), some degrees of retinal immaturity or ROP were considered compatible with discharge home of an infant requiring oxygen therapy, and in the remaining 71 (46%), there were no ROP findings that would prevent discharge home for an infant requiring oxygen therapy. The latter group did, however, note that follow-up and/or home monitoring of oxygen would be modified according to the severity of the ROP findings.

Among the 349 institutions reporting that they have discharged home infants requiring oxygen, the oxygen was usually administered per nasal cannula, ordered in liters per minute (n=339, 97%), although a specified fraction of inspired oxygen (Flo₂) was sometimes used (n=38, 11%) (the total exceeds 100% because more than one type of prescription was reported by 46 centers). Seventeen centers (5%) reported

other types of oxygen prescription as

The FIO₂ delivered by the equipment at home was monitored by visiting paramedical personnel intermittently in 127 (36%) centers, and parents checked FIO₂ levels regularly in 47 (13%). Twentyfour centers (7%) reported other means of FIO₂ monitoring. In addition, infants receiving oxygen were usually monitored at home on an apnea and/or bradycardia monitor (n = 279, 80%).

Home monitoring of the infants' arterial oxygenation status was more varied. Among the 351 centers that reported using home oxygen, visiting paramedical personnel checked pulse oximetry on a periodic basis at home in 137 (39%). In 65 centers (19%), parents used pulse oximetry at home regularly, while in 36 (10%), the infants' oxygenation status was monitored at home solely by observing for cyanosis (in the remaining centers this question was not answered.)

In follow-up outpatient visits, the continued need for oxygen was assessed by observation of color only in 149 centers (43%), while pulse oximetry or transcutaneous Pao₂ measurements were obtained in 199 (57%). Blood gas measurements were not reported in the outpatients.

When pulse oximetry saturation was used, 40% of those centers surveyed reported minimum (n = 167) or maximum (n = 130) pulse oximetry criteria for infants with chronic lung disease. These are shown below:

Minimum Saturation	
Criteria of Responders	No. (%)
Over 85%	32 (19)
• Over 88%	29 (17)
• Over 90%	79 (47)
Over 92%	20 (12)
Over 94%	5 (3)
Other	3 (2)
Maximum Saturation	
Criteria of Responders	No. (%)
Under 94%	32 (24)
Under 96%	52 (40)
Under 97%	7 (5)
Under 98%	13 (10)
Under 99%	3 (2)
Under 100%	4 (3)
No upper limit	20 (15)

The majority seek to keep the pulse oximetry between 90% to 95% saturation, although the range of stated goals extended from 85% to no upper limit.

Several comments were received on the questionnaires. The most frequent one expressed the extremely rare occurrence of ROP or eye immaturity remaining at the time one might discharge home an infant with chronic lung disease requiring oxygen, and disbelief that this could be a significant problem (n = 12). The other comments revealed frustration with the lack of data available for pulse oximetry guidelines in older premature infants.

Comment.-While there are data showing that 4 weeks of routine high inspired oxygen (regardless of need) following birth will increase the number of cases of severe ROP,3 there are minimal data about safe or dangerous levels of oxygen for the retina during the later, long weeks of ROP regression.4 The wide range of practices reported in the questionnaires reflects this lack of data. There is presently no established safe upper limit of oxygenation in regard to the immature retinal vessels. The wide range of lower limits of acceptable saturation similarly reflects a lack of consensus over the data on those limits in regard to chronic lung disease and growth.

To answer these concerns, an investigation of infants with immature retinas who are randomly assigned to treatment with different oxygen-monitoring goals would be needed. Such a study would enable neonatologists to administer oxygen more safely to infants with chronic lung disease both in the hospital and at home. Due to the infrequent occurrence of severe ROP, such a study will have to be multicentered to reach a conclusion within a reasonable period of time.

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Nail Shedding in Kawasaki Syndrome

Sir.—Kawasaki syndrome (KS) is a multisystem disorder of unknown origin first described in Japan in 1967. Since then, distinctive clinical features have been recognized. We describe a patient with KS who developed an unusual nail feature not previously noted.

Patient Report. - A 4-year-old white boy was listless and anorectic, with the onset of conjunctivitis 7 days prior to admission (PTA) to the hospital. He had a high constant temperature of 40°C (rectal), with minimal response to antipyretics 6 days PTA and large tender anterior cervical nodes 5 days PTA. A bright red nonraised rash developed on the bridge of his nose, palms, and ankles 4 days PTA that became generalized within 24 hours. He received amoxicillin, acetaminophen, and a combination product of brompheniramine maleate and phenylpropanolamine hydrochloride (Dimetapp). One day PTA, he developed diarrhea with associated headache, sore throat, and edema of the hands and feet. His symptoms continued, with discomfort out of proportion to his physical findings, at which point he was transferred to our hospital.

On admission, his blood pressure was 112/60 mm Hg, his temperature was 39.8°C (rectal), he had a pulse rate of 140 beats per minute, and his respiratory rate was 28/min. He was uncomfortable and irritable. He complained of mild skin, muscle, and joint pain. There was mild conjunctivitis with periorbital edema and desquamation of the right eyelid and right ear. His cheeks were flushed and there was peeling and cracking of the lips. The pharynx was injected, with a small amount of whitish exudate visible. The tongue was red. A tender left anterior cervical node was present. There was diffuse abdominal tenderness to the slightest palpation. The skin showed a diffuse generalized erythematous nonscaling rash, including the palms and soles. Mild erythema of the urethral meatus was present as well as a nonpitting edema of the hands and feet. Laboratory studies were consistent with the diagnosis of KS, and there were no other abnormalities.

Following admission, the patient had intermittent temperatures of 39°C to 40°C, which lasted for 2 weeks. He was treated with aspirin to maintain a therapeutic level of 20 to 25 ng/dL, and there was a slow lowering of the temperature over a 14-day period. The aspirin was then tapered to a dose of 10 mg/kg per day. Approximately 1 week after admission to the hospital, the rash faded and disappeared, replaced by desquamation at the fingertips and marked swelling of the hands, feet, scrotum, and abdomen, with associated itching and discomfort that resolved spontaneously after 7 days. Following this, he developed marked swelling of the knees and right elbow, which gradually improved. He was discharged on the 20th hospital day.

When examined 36 days after discharge

from the hospital, the patient's old fingernails were halfway shed, with the proximal part of the nail beds occupied by new nails. The toenails were in a similar condition, except that the old toenails were only a fourth of the way shed. When the patient was seen 50 days after discharge, the old fingernails were fully shed and there were brand new fingernails. The old toenails were halfway shed. His platelet count was $497 \times 10^9 / L$. Follow-up electrocardiogram, echocardiogram, and chest roentgenogram were normal.

Comment.—Most of the characteristic clinical and laboratory findings of KS were observed in this patient. In addition, there were nail changes to our knowledge not previously reported in this condition that were observed after recovery from the illness. While the development of nail abnormality in the form of Beau's lines is almost universally seen in KS, total and symmetrical shedding of all the nails of both fingers and toes is unusual and had not been previously described.

Beau's lines are transverse depressions or grooves that occur on the nail following temporary interference with nail formation. All nails of the fingers and toes may be affected several weeks or more after the onset of the primary disease. Beau's lines have been described in many patients with severe systemic diseases, zinc deficiency, carpal tunnel syndrome, traumatic nail injury, and dermatitis of the skin adjacent to the nail, and in patients who have suffered severe cold temperatures.³

Shedding of the nail, also called onychomadesis or defluvium unguium, is an actual separation and shedding of the whole nail with associated new nail formation, as seen in this patient. Normally, nails grow continuously throughout life and are not shed. If they are shed, the replacement grows at the same rate as normal. The growth of fingernails, however, is normally faster than that of toenails.

Onychomadesis has been described in many conditions, including after nail trauma, in an inherited developmental anomaly with an autosomal dominant character, following bullous eruptions of digital tips, and with the use of large doses of certain medications such as cloxacillin and cephaloridine.³

Nail shedding should not be confused with onycholysis, which is a painless mere separation of the nail from its bed without apparent cause. It usually starts at the tip of the nail and progresses until one third of the affected nail is loose. The nail, however, would be normal otherwise. In contrast, in on-

ychomadesis the nail initially separates at its proximal part and may progress distally. Onycholysis is almost always confined to women and a common cause of it is psoriasis, although it may be seen in conjunction with other diseases.

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Neonatal Nasal Obstruction Associated With Methyldopa Treatment During Pregnancy

Sir.—Methyldopa is used frequently in the long-term management of hypertension in pregnancy because of its documented effectiveness and relative lack of fetal toxicity. Although not reported in neonates, nasal congestion is a known side effect of methyldopa in 1% to 3% of adults and children receiving long-term therapy. We report an association between maternal administration of methyldopa and neonatal nasal obstruction.

Patient Reports. - PATIENT 1. - A 38year-old gravida 3, para 1, aborta 1 woman underwent an elective cesarean section at 39 weeks' gestation because of frank breech fetal position, maternal hypertension, and advanced maternal age. She was treated with methyldopa (250 mg orally twice a day) since the eighth week of gestation. At delivery, a loop of cord was noted around the neonate's neck and there was moderate difficulty in delivering the head. The Apgar scores were 3, 8, and 9 at 1, 5, and 10 minutes, respectively, and the birth weight was 3660 g. No signs of facial or nasal trauma were evident. In the delivery room, the neonate was found to be "snuffly" prior to insertion of nasal catheters. Occlusion of the mouth caused severe respiratory distress; however, the right and left nares were patent to insertion of an 8F feeding tube. By 6 hours of age, the signs of nasal obstruction progressed to the point where an oropharyngeal airway was placed. Respiratory distress promptly resolved. There were no repeated attempts at suctioning the nares. Examination by an ear, nose, and throat specialist revealed bilateral edematous nasal mucosa that was severe enough to reduce the passages to a narrow slit. Examination findings were otherwise normal. The neonate was treated with 1 to 2 drops of 0.5% xylometazoline hydrochloride nasal solution every 6 hours. An attempt to remove the airway at 28 hours failed; however, it was discontinued permanently by 34 hours. There were no further signs of nasal obstruction, and topical vasoconstrictors were discontinued.

PATIENT 2. - A 30-vear-old gravida 2. para 0, aborta 1 woman was treated for moderate hypertension with methyldopa (500 mg orally three times a day) from the first trimester to the postpartum period. The pregnancy was otherwise uneventful. At 36 weeks' gestation, a 3230-g female neonate was delivered via a nontraumatic spontaneous vaginal delivery through thick meconium. No meconium was present below the cords on direct laryngoscopic visualization. The Apgar scores were 7 and 8 at 1 and 5 minutes, respectively. The neonate was tachypneic prior to suctioning of the nares. Within 9 hours, this progressed to considerable nasal obstruction and respiratory distress. At this point, the nares were suctioned with no relief. Physical examination by an ear, nose, and throat specialist revealed marked nasopharvngeal edema and no other abnormalities. The remainder of the physical examination findings were within normal limits. A chest roentgenogram and capillary blood gas test results were normal. The infant was initially treated with oxygen and a 0.25% phenylephrine hydrochloride nasal solution, with transient relief. Progression of signs of respiratory distress prompted use of a No. 00 oropharyngeal airway at 20 hours of age and transfer to the neonatal intensive care unit. Phenylephrine was changed to 0.5% xylometazoline hydrochloride nasal solution, 1 to 2 drops every 6 hours. Gradual resolution of the nasal obstruction occurred. The airway was removed at 44 hours of age, and topical vasoconstrictors were discontinued.

Comment. - Methyldopa is known to cross the placenta with fetal serum concentrations similar to the maternal serum concentrations. 3,4 Nasal congestion occurs in chronic methyldopa therapy in both adults and children, although it has not been reported in neonates.5 Hans and Kopelman1 reported no complications in 11 surviving neonates born to mothers receiving low-dose methyldopa. Mutch et al2 described a tendency for the neonates to have smaller head circumferences and to require prolonged tube feeding. Of the 9 patients studied by Jones et al,4 1 full-term neonate developed respiratory distress of unknown origin. Some of the patients described by the above authors were born prematurely, and respiratory distress syndrome could have masked the signs of nasal obstruction.

A 5-year review of our medical records failed to reveal any other instances of neonatal nasal obstruction. The possibility that traumatic nasal suction in the delivery room was the cause

of obstruction in our two patients is

highly unlikely.

We conclude that intrauterine exposure to methyldopa may be a rare cause of significant neonatal nasal obstruction. The differential diagnosis of nasal obstruction in neonates should include maternal treatment with methyldopa. Similar patient reports, animal experiments, and prospective clinical studies will be needed to substantiate this association.

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Placental Transfer of Flecainide

Sir.—Flecainide, a local anesthetictype antiarrhythmic agent, has recently been approved for use in the United States. To augment the little available information regarding its use during pregnancy and effects on the neonate, we present the following patient report.

Patient Report.—A 24-year-old woman, gravida 5, para 1-0-3-1, presented at 37 weeks' gestation with spontaneous rupture of membranes. Review of her medical history revealed mitral valve prolapse with moder-

ate to severe mitral regurgitation. In the fifth month of her pregnancy she began taking metoprolol for increasingly symptomatic supraventricular tachycardia, with an initial good response. By 35 weeks' gestation, however, the patient's symptoms had worsened; a repeated electrocardiogram at that time disclosed Wolf-Parkinson-White syndrome, type A. Administration of metoprolol was discontinued, and she began taking flecainide, 100 mg by mouth two times per day; the dosage was subsequently increased to 150 mg two times per day, with symptomatic improvement.

Continuous fetal heart rate monitoring after admission revealed no evidence of distress, and approximately 11 hours after admission the patient delivered a viable female infant with Apgar scores of 9 and 10 at 1 and 5 minutes, respectively. Blood samples drawn simultaneously at delivery revealed a maternal venous flecainide level of 0.63 mg/L and an umbilical venous flecainide level of 0.44 mg/L (high-pressure liquid chromatography, Roche Biomedical Laboratories, Nutley, NJ).

An electrocardiogram performed on the infant at 90 minutes of age revealed normal sinus rhythm, 120 beats per minute, a P-R interval of 0.13 seconds, and a QRS interval of 0.05 seconds (QTc interval of 0.40 seconds), all of which are normal for age. Blood pressure, not routinely monitored in term infants in our institution, was not recorded, but examination revealed good perfusion as evidenced by capillary refill and skin color.

Comment. - Flecainide is a member of the subclass IC of antiarrhythmic agents and has the ability to markedly suppress nonsustained ventricular arrhythmias. Although flecainide was originally approved for use in patients with life-threatening premature ventricular complexes and symptomatic nonsustained ventricular arrhythmias, the US Food and Drug Administration has recently restricted its indications to the treatment of life-threatening arrhythmias, such as sustained ventricular tachycardia. Major effects on the electrocardiogram include prolongation of the P-R and QRS intervals, both of which are routinely seen during therapy with the drug. In normal adult volunteers, hemodynamic effects at therapeutic levels (0.2 to 1.0 mg/L) include reduced cardiac output and increased heart rate. Extensive reviews of the pharmacologic properties of the drug are available elsewhere.2

In the patient reported on above, simultaneous sampling revealed that flecainide readily crossed the placenta, resulting in an umbilical venous level that was 69% of the simultaneous maternal venous level. The efficacy with which flecainide crosses the placenta has not previously been reported, but this level

is consistent with previous reports of transplacental transfer of similar compounds.³

Perry et al recently reported their experience with the use of flecainide in the pediatric population; of note was a low incidence of transient hyperactivity as a side effect in patients aged 3 years or less. Given the efficacy with which flecainide crosses the placenta, it should be considered as a causative factor in the differential diagnosis of newborn hyperactivity, when appropriate.

In summary, we have reported on a patient who received flecainide during the late third trimester and delivery. Despite the ready attainment of therapeutic levels of flecainide in the neonate, we were unable to demonstrate any effects on the neonatal electrocardiogram or hemodynamics. Due to the lack of well-controlled studies in pregnant women, however, caution is urged in prescribing flecainide in this population.

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Aseptic Meningitis Associated With Administration of Trimethoprim and Sulfamethoxazole

Sir.—Aseptic meningitis is common and is usually caused by a viral infection. However, other infectious and noninfectious causes of aseptic meningitis are legion.¹ Aseptic meningitis apparently induced by trimethoprim and sulfamethoxazole has been reported in at least five adult patients, 26 but to my knowledge it has not yet been reported in children. I present a child in whom recurring aseptic meningitis appeared to have been caused by trimethoprim and sulfamethoxazole.

Patient Report. - A 6-year-old boy was admitted with fever, vomiting, and nuchal rigidity. He had a history of otitis media 2 weeks prior to admission that had been treated with amoxicillin; 1 day prior to admission the amoxicillin therapy was discontinued, and administration of trimethoprim and sulfamethoxazole was begun. Several hours after the first dose of trimethoprim and sulfamethoxazole, vomiting developed, followed by fever and stiff neck. At that time, the patient appeared acutely ill with nuchal rigidity and an oral temperature of 37.8°C. Examination of cerebrospinal fluid (CSF) showed 44 white blood cells per microliter. with 0.80 polymorphonuclear leukocytes, 0.20 mononuclear cells, a glucose concentration of 3.3 mmol/L, and a protein concentration of 0.40 g/L. Results of a Gram stain and latex agglutination tests of the CSF and urine were negative for Haemophilus influenza, Neisseria meningitidis, and Streptococcus pneumoniae; a subsequent culture was negative for bacteria. Throat cultures of the patient and his immediate family were negative for N meningitidis. Because of pretreatment, he was given 10 days of intravenous ceftriaxone sodium and had an uneventful recovery.

Three months later otitis media recurred. The patient was again given trimethoprim and sulfamethoxazole, and within 2 hours he complained of headache and stiff neck and had a temperature of 38.3°C and nuchal rigidity. Examination of CSF revealed 24 white blood cells per microliter, with 0.20 polymorphonuclear leukocytes and a normal glucose concentration but a protein concentration of 0.70 g/L. A repeated lumbar puncture after 24 hours showed 125 white blood cells per microliter, with 0.44 polymorphonuclear cells and normal glucose and protein concentrations. Quantitative immunoglobulin levels and the total serum complement and the results of urine counterimmunoelectrophoresis and a latex agglutination test of the CSF were normal. Computed tomograms of the head showed no obvious fractures, and thin slices of the middle ear were normal. Slitlamp examination showed no uveitis. Viral cultures of the throat, rectum, and CSF were negative, and acute and convalescent serum specimens were negative for influenza A and B antibodies. The patient was given intravenous antimicrobial agents pending the results of cultures of the blood and spinal fluid.

I then discovered that aseptic meningitis associated with trimethoprim and sulfamethoxazole had been reported in the adult literature. The therapy was switched to oral antimicrobial agents, and the patient was discharged. Recovery was uneventful. The parents refused a repeated trial of trimethoprim and sulfamethoxazole to confirm the diagnosis. There were no recurrences of meningitis in the 2 years after the episode.

Comment.—Aseptic meningitis associated with the use of trimethoprim and sulfamethoxazole has been reported in adults, but I believe this is the first reported pediatric case. All other

causes of aseptic meningitis have not been definitively excluded, but the immediate temporal relationship to trimethoprim and sulfamethoxazole and the recurring nature of this illness argue for a hypersensitivity reaction to trimethoprim and sulfamethoxazole. Derbes' reported that a patient developed meningitis after exposure to trimethoprim alone, suggesting that the CSF reaction may be specific to this antimicrobial agent. The mechanism of druginduced meningitis is unknown, although it has been suggested that it may develop as the result of an immediate hypersensitivity reaction "rather than through the induction of antitissue antibodies or the elaboration of other humeral factors, such as immune complexes."3

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Respiratory Distress Secondary to Subacute Thyroiditis

Sin—Thyroid disease is an uncommonly reported cause of acute respiratory distress in childhood. Subacute thyroiditis (SAT) occurs infrequently in children. To our knowledge, it has not been previously implicated as a cause of respiratory insufficiency. We describe a child in whom thyroid enlargement during an episode of SAT resulted in respiratory compromise.

Patient Report.—A 5-year-3-month-old girl was admitted to Children's Hospital of New Jersey, Newark, because of progressive dysphagia, hoarseness, and a history of stridor. Four days prior to admission she had a sore throat, an earache, and a temperature of 38.8°C; she was examined and was found to have pharyngitis. A throat culture was obtained, and she was started on treatment with oral penicillin V (Pen VK). The day prior to admission, her mother

noted diffuse swelling of the anterior aspect of the neck associated with tenderness, hoarseness, stridor, and difficulty in swallowing. There was no history of irritability, palpitations, weight loss, heat intolerance, or diarrhea and no medical history of respiratory or thyroid diseases.

The patient appeared alert and apprehensive without stridor or labored breathing. Her oral temperature was 38.8°C. Her heart rate was 140 beats per minute, respiratory rate was 24/min, and blood pressure was 96/54 mm Hg. Her weight was 20.9 kg (75%) and her height, 112.5 cm (75%). She had limited neck mobility and extreme tenderness to palpation, especially on the left side of the neck. The circumference of her neck was 29.5 cm. Bilateral anterior cervical nontender lymphadenopathy was present. The tonsils were erythematous with exudates. There were no audible adventitial sounds in her lungs. The rest of the examination showed normal results.

Her white blood cell count was 17×10^{9} /L, with 0.82 polymorphonuclear cells, 0.02 band forms, 0.11 lymphocytes, 0.05 monocytes, and 0.02 atypical lymphocytes. Her erythrocyte sedimentation rate was 109 mm/h, and serum electrolyte levels were normal. A lateral neck roentgenogram revealed a homogeneous soft-tissue swelling on the anterior aspect of the neck. The epiglottis was normal. No foreign object or abscess was noted.

On admission, a thyroid scan was scheduled. However, the patient experienced respiratory distress with a respiratory rate of 60/min and inspiratory stridor. She required intubation without mechanical ventilation for maintenance of a patent airway. A computed tomographic scan of the neck revealed a well-defined, enhancing, anterior, left-sided, soft-tissue mass involving the thyroid gland and displacing the trachea to the right. On ultrasound examination, a diffusely enlarged noncystic thyroid gland was identified. A thyroid aspirate was obtained, and parenteral antibiotic therapy was initiated.

Within 2 days the tenderness in her neck and the size of her thyroid gland decreased (neck circumference, 28.5 cm), and she became afebrile. She was extubated after 48 hours and received a 10-day course of antibiotics. Throat, thyroid aspirate, and blood cultures were sterile. Thyroid function tests were obtained during hospitalization (Table). Antithyroglobulin antibodies and thyroid microsomal antibodies were negative, and the serum thyroglobulin level was 15.2 μg/L on day 1 (normal, 11 to 36 μg/L).

The patient has had no thyromegaly and normal thyroid function test results for 2 years, and there were no further recurrences of SAT.

Comment.—Textbooks of pediatrics mention thyroid enlargement among the potential causes of inspiratory stridor. However, no mention is made

Sequential White Blood Cell Values, Erythrocyte Sedimentation Rates, and Thyroid Function Tests

Day	White Blood Cell Count, ×10³/L	Erythrocyte Sedimentation Rate, mm/h	Thyroxine Radioimmunoassay, mmol/L (64-154)*	Thyrotropin, mU/L (0-6)*
1	17	109	171	1.3
5			82	2.9
10	5.4	79	63	3.7
19	5.8	21	104	1.0
Outpatient (7 mo after discharge)			127	2.2

^{*}Numbers in parentheses indicate normal ranges.

of acute inflammation of the thyroid gland as a cause of respiratory distress. 1,2 There are reports of three children who developed respiratory distress requiring intubation during episodes of acute suppurative thyroiditis. 2,5 We are unaware of any reports of children with SAT who developed respiratory problems. The differential diagnosis considered for our patient included acute suppurative thyroiditis, a hemmorhagic thyroid cyst, and SAT.

Acute suppurative thyroiditis 5-9 is usually caused by bacteria that can be identified by throat and blood cultures. The left lobe of the thyroid gland is generally affected, and abscess formation is common. Thyroid function tests usually have normal results. Our patient had no evidence of bacterial infection or abscess formation; therefore, the diagnosis of acute suppurative thyroiditis is less likely. Hemorrhage into a preexisting cyst may present with symptoms similar to those seen in our patient.10 However, she had no evidence of a thyroid cyst on examination by ultrasound, computed tomographic scan, or aspiration of the mass.

Our patient's findings were consistent with SAT. Her symptoms (fever, sore throat, earache, hoarseness, and dysphagia) are characteristic of thyroiditis. 11,12 Pharyngitis is commonly found in patients with SAT. 11 Common cold, influenza, Epstein-Barr, measles, 12 and mumps viruses, 13,14 adenovirus, 15 and coxsackievirus 12 have been implicated as causes of SAT. Coxsackieviruses are the most common infectious agents encountered.

Patients with SAT may present with initial symptoms of hyperthyroidism. Initial thyroid function tests usually confirm hyperthyroxinemia. Subsequent thyroid function test results are

usually normal. 16 Often, a brief period of chemical hypothyroidism may intervene. Initial radioactive iodine uptake, which we were unable to assess in our patient, is usually suppressed. Our patient did demonstrate initially high, then low, and subsequently normal serum thyroxine levels (Table).

In summary, we encountered a child who developed respiratory compromise as a result of SAT. We think that it is important to consider thyroiditis among the causes of respiratory distress. Children who have acute inflammation of the thyroid gland should be monitored for the possible occurrence of respiratory difficulties.

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The Management of Umbilical Granulomas With Cryocautery

Sin-Umbilical granuloma is a common, self-limiting, moist granulating area at the base of the cord with a slight mucoid or mucopurulent discharge. Traditional management varies from benign indifference to chemical or electric cauterization to excision.

We have favorably used cryocauterization for umbilical granuloma and compared this technique with chemical and electric cauterization.

Patients and Methods. - Seventy-five infants between 20 and 60 days of age from the clinic of one of the authors (S.S.S.) and KEM Hospital, Bombay, India, with umbilical granulomas of 7 to 15 mm in size were treated on an outpatient basis either by cryosurgery, electrocautery, or an application of silver nitrate between May 1977 and June 1987 in a prospective clinical trial using a randomized protocol. After local cleaning, the infant was firmly held by a nurse while the general-purpose cryoprobe (Wallach Surgical) with nitrous oxide as a refrigerant was applied directly to the granuloma for 3 minutes; contact with normal skin was avoided. An ice ball extended 2 to 3 mm beyond the contact site. On completion, the treated site was cleansed and left dry and open and the infant was sent home.

A bipolar electrosurgical cautery with a 50-W output was used in 25 infants and the granuloma was coagulated until the tissue charred. The infant was sent home soon after the procedure. In another 25 infants, the granuloma was chemically cauterized by applying the silver nitrate stick to the site until a white eschar formed. No medication or anesthesia was used in any of

Comparative Results of Treating Umbilical Granulomas With Cryosurgery, Electrocautery, and Chemical Cauterization

	No. of Patients				
	Depigmentation	Foul- Smelling Discharge	Needed Multiple Applications	Cured/ Normal	
Cryosurgery (n = 25)	20	1	0	25	
Electrocautery (n = 25)	0	6	4	21	
Chemical cauterization (n = 25)	0	3	5	20	

these groups. A follow-up examination was performed at the end of 1, 4, and 24 weeks.

Results.—Results are summarized in the Table. At the end of 1 week, the granulomas in the cryocauterized group were shrunken, with redness and a slight sticky white discharge in 17 infants, and necrotic tissue in the process of being separated was noted in the remaining 8 infants. At 4 weeks, the umbilicus returned to normal in all infants except for a periumbilical ring of depigmentation of 1 to 3 mm in 20 of 25 infants that resolved within 6 months.

Foul discharge and failure rates

were higher with electrocauterization and silver nitrate therapy though statistically insignificant ($\chi^2 = 3.56$, more than 70.5). While results were satisfactory with all three modalities, healing was more rapid with cryocauterization. There were no complications with cryocauterization. Reapplication of cryosurgery was unnecessary.

Comment.—Cryocauterization has been successfully used in gynecology for a variety of indications, including posthysterectomy granulation tissue on the vaginal vault.^{1,2} These data stimulated us to attempt treatment of

umbilical granulomas by cryocauterization.3

Cryocautery, though more expensive and complex, demonstrated superior results in our limited study. We encourage the use of cryosurgery as an alternative treatment for umbilical granulomas and encourage others to investigate this modality in a larger series.

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Special Contribution

Harold E. Harrison

Harold E. Harrison died October 2, 1989, at the age of 81 years, after a brief, rapidly progressing illness. His passing ends a career virtually synonymous with the best of pediatrics in the 20th century. He brought excellence and rich contributions to every major type of endeavor in pediatrics from his formative years until the last months of his life.

Together with his wife Helen, he advanced science through the application of chemistry to problems of calcium, phosphorus, and vitamin D. These studies helped to illuminate this field with contributions over more than a 50-year period, including some now to appear posthumously. These achievements have been noted by the academic community by several awards, most notably the Howland Award to Harold and Helen jointly.

As a teacher, Harrison also trained two generations of pediatric residents both at his home institution, the Baltimore City Hospitals, and at The Johns Hopkins Hospital following earlier stays at Yale and New York Hospital. His teaching tools consisted of knowledge, analytic skill, open mindedness, personal modesty, and great kindness. The store of knowledge was always immense, varied, and current. His ability at the bedside marked him as without peer over several decades. He always listened carefully to others. and when he did not accept an idea or suggestion, his rejection was always well articulated and gracious. He also knew when to ask for help and, though rarely necessary, to acknowledge error. The patient always came first in every sense of the concept. No unnecessary pain to test a pet idea, no inconvenience to patient or family to satisfy a personal need. Even to advance science, inconvenience only with consent, long before there were review boards at medical institutions.

He took seriously his role of advocate for children in many ways, including defending and supporting individuals and, most importantly, raising the consciousness of the Baltimore community to health care issues, then persevering until the goals were achieved. These ranged from lead poisoning to communicable disease to care for foster children. I would include in this part of the legacy his meticulous, thoughtful training of residents who went to practice pediatrics in the United States and in other parts of the world inspired by the qualities of their chief and imbued with some of his traits and skills. These men and women will carry ideals and commitment into the next century.

It is well worth our time for a moment's pause to honor Harold one more time as the quintessential pediatrician and reflect on how we may continue to follow the many trails he blazed for us. He would wish us to continue in the interest of science and for the benefit of children.

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NEW FROM McNEIL

Ibuprofen Suspension 100 mg/5 ml

A new therapeutic alternative for fever

Antipyretic efficacy

In children with temperatures greater than 102.5°F, ibuprofen 10 mg/kg is more effective than ibuprofen 5 mg/kg or acetaminophen 10 mg/kg!

PediaProfen is indicated for the reduction of fever in children 6 months and older.

· Longer duration of action than acetaminophen for fever^{1,2}

Ibuprofen 10 mg/kg provides up to 8-hour relief. That means fewer interruptions in the family's work, school, or sleep schedules.

Safety profile*

See brief summary of Prescribing Information. Significant adverse effects are reported with NSAIDs. Serious as well as minor side effects can occur with long-term use of high-dose ibuprofen. In clinical studies with over 400. pediatric patients, no significant adverse reactions were reported during short-term therapy for fever.2

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Designed for compliance; well liked by patients in clinical studies?

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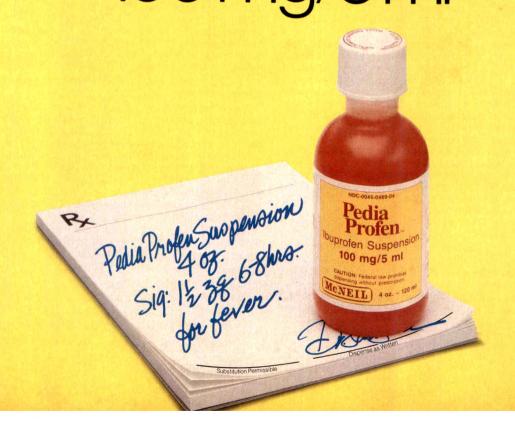
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From the children's fever relief specialist

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A new therapeutic alternative for fever

New Pedia Profen...
Ibuprofen Suspension 100 mg/5 ml

The following is a brief summary only. Before prescribing, see complete prescribing information in **PediaProfen** labeling.

INDICATIONS AND USAGE: PediaProfen is indicated for the reduction of fever in patients aged 6 months and older, and for the relief of mild-to-moderate pain in patients aged 12 years and older.

CLINICAL PHARMACOLOGY: Controlled clinical trials comparing doses of 5 and 10 mg/kg ibuprofen and 10-15 mg/kg of acetaminophen have been conducted in children 6 months to 12 years of age with fever primarily due to viral illnesses. In these studies there were no differences between treatments in fever reduction for the first hour and maximum fever reduction occurred between 2 and 4 hours. Response after 1 hour was dependent on both the level of temperature elevation as well as the treatment. In children with baseline temperatures at or below 102.5°F both ibuprofen doses and acetaminophen were equally effective in their maximum effect. In those children with temperatures above 102.5°F, the ibuprofen 10 mg/kg dose was more effective. By 6 hours children treated with ibuprofen 5 mg/kg tended to have recurrence of fever, whereas children treated with ibuprofen 10 mg/kg still had significant fever reduction at 8 hours. In control groups treated with 10 mg/kg acetaminophen, fever reduction resembled that seen in children treated with 5 mg/kg of ibuprofen, with the exception that temperature elevation tended to return 1-2 hours earlier.

CONTRAINDICATIONS: PediaProfen should not be used in patients who have previously exhibited hypersensitivity to ibuprofen, or in individuals with all or part of the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents. Anaphylactoid reactions have occurred in such patients.

WARNINGS: Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy. Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastrointestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

PRECAUTIONS: General: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints while receiving PediaProfen, the drug should be discontinued and the patient should have an ophthalmologic examination which includes central visual fields and color vision testing.

Fluid retention and edema have been reported in association with ibuprofen, therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension.

PediaProfen, like other nonsteroidal anti-inflammatory agents, can inhibit platelet aggregation, but the effect is quantitatively less and of shorter duration than that seen with aspirin. Ibuprofen has been shown to prolong bleeding time (but within the normal range), in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying hemostatic defects, PediaProfen should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients on PediaProfen should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

In order to avoid exacerbation of disease of adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ibuprofen is added to the treatment program.

The antipyretic and anti-inflammatory activity of PediaProfen may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Since ibuprofen is eliminated primarily by the kidneys, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation. Prospective studies on the safety of ibuprofen in patients with chronic renal failure have not been conducted.

Safety and efficacy of PediaProfen in children below the age of 6 months has not been established.

Pregnancy: Reproductive studies conducted in rats and rabbits at doses somewhat less than the maximal clinical dose did not demonstrate evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. As there are no adequate and well-controlled studies in pregnant women, this drug should be used during pregnancy only if clearly needed. Because of the known effects of nonsteroidal antiinflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during late pregnancy should be avoided. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats. Administration of PediaProfen is not recommended during pregnancy

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with ibuprofen is gastrointestinal. In controlled clinical trials, the percentage of adult patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

Adverse reactions occurring in 3% to 9% of patients treated with ibuprofen: nausea, epigastric pain, heartburn, dizziness, rash. Adverse reactions occurring in 1% to 3% of patients: diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract, headache, nervousness, pruritus, tinnitus, decreased appetite, edema, fluid retention (generally responds promptly to drug discontinuation). Still other reactions (less than 1 in 100) have been reported, and are detailed in the full summary of prescribing information.

DOSAGE AND ADMINISTRATION: Shake well prior to administration.

Fever Reduction in Children 6 months to 12 years of age: Dosage should be adjusted on the basis of the initial temperature level (See CLINICAL PHARMACOLOGY for a description of the controlled clinical trial results). The recommended dose is 5 mg/kg if the baseline temperature is less than 102.5°F or 10 mg/kg if the baseline temperature is greater than 102.5°F. The duration of fever reduction is generally 6-8 hours and is longer with the higher dose. The recommended maximum daily dose is 40 mg/kg.

Mild to moderate pain: 400 mg every 4 to 6 hours as necessary for the relief of pain in adults.

In controlled analgesic clinical trials, doses of ibuprofen greater than 400 mg were no more effective than 400 mg dose.

HOW SUPPLIED: PediaProfen Ibuprofen Suspension 100 mg/5 ml (teaspoon)-

orange, berry-vanilla flavored

Bottles of 4 oz (120 ml)......NDC 0045-0469-04 Bottles of 16 oz (480 ml)......NDC 0045-0469-16

SHAKE WELL BEFORE USING. Store at room temperature. Caution: Federal law prohibits dispensing without prescription.

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Leads From the MMWR

Morbidity and Mortality Report Centers for Disease Control, Atlanta

Current Trends CDC Criteria for Anemia in Children and Childbearing-Aged Women

HEMOGLOBIN (Hb) and hematocrit (Hct) measurements are the laboratory tests used most commonly in clinical and public health settings for screening for anemia. Because most anemia in children and women of childbearing age is related to iron deficiency,1 the main purpose of anemia screening is to detect those persons at increased risk for iron deficiency. Proper anemia screening requires not only sound laboratory methods and procedures but also appropriate Hb and Hct cutoff values to define anemia. The "normal" ranges of Hb and Hct change throughout childhood and during pregnancy, and are higher for men than women. 1,2 Thus, criteria for anemia should be specific for age, sex, and stage of pregnancy. Current major reference criteria for anemia, however, are not based on representative samples and fail to take into account the normal hematologic changes occurring during pregnancy. To address these limitations, CDC has formulated new reference criteria for use in clinical practice for public health and nutrition programs and the CDC Pediatric and Pregnancy Nutrition Surveillance Systems. The new criteria may also be useful for defining anemia in clinical research and nutrition surveys.

The anemia reference values for children, nonpregnant women, and men are derived from the most current nationally representative sample-the Second National Health and Nutrition Examination Survey, 1976-1980 (NHANES II). Because representative data are not yet available for pregnant women, anemia reference values are based on the most current clinical studies available. Adjustment values of Hb and Hct cutoffs are provided for persons who reside at higher altitudes and for those who smoke cigarettes.

Anemia Cutoffs for Children, Nonpregnant Women, and Men

Because hematologic values normally change as children grow older,

it is necessary to use age-specific criteria for diagnosing anemia in children. The best hematologic reference data for the United States are available from the NHANES II. The Hb and Hct cutoffs recommended represent the age-specific fifth percentile values for "healthy" persons from NHANES II (Table 1).^{3,4} The healthy sample was defined by excluding persons who were likely to have iron deficiency based on multiple iron biochemical measures. The anemia cutoff values based on these NHANES II studies for younger children are in close agreement with the cutoff values recommended by the American Academy of Pediatrics, which were based on a sample of healthy white middleclass children. 5 Even though no data are available from NHANES II to determine anemia cutoffs for infants less than 1 year of age, cutoff values for children 1-2 years can be extrapolated back to 6 months of age. In general, anemia screening to detect iron deficiency is not indicated for infants less than 6 months of age because younger infants usually have adequate iron nutritional status.6

Anemia Cutoffs during Pregnancy

During a normal pregnancy, a woman's hematologic values change substantially.2 For women with adequate iron nutrition, Hb and Hct values start to decline during the early part of first trimester, reach their nadir near the end of second trimester, then gradually rise during the third trimester. 2,7-10 Because of the change of Hb and Hct during pregnancy, anemia must be characterized according to the specific stage of pregnancy. The normal range of Hb and Hct during pregnancy is based on data aggregated from four European studies of healthy iron-supplemented pregnant women.7-10 These studies provide similar findings at each specific month of pregnancy. The month-specific fifth percentile values for Hb of the pooled data have been

adopted for use in the CDC Pregnancy Nutrition Surveillance System (Table 2). In addition, trimester-specific cutoffs also have been developed for use in the clinical setting (Table 2). These trimester-specific cutoffs are based on the mid-trimester values; cutoffs for the first trimester, the time at which most women are initially seen for prenatal care, are based on a late-trimester value.

Adjustment of Hb and Hct Cutoffs for Altitude and Smoking

Persons residing at higher altitudes (greater than 1000 meters [3300 feet]) have higher Hb and Hct levels than those residing at sea level. This variation is due to the lower oxygen partial pressure at higher altitudes, a reduction in oxygen saturation of blood,11 and a compensatory increase in red cell production to ensure adequate oxygen supply to the tissues. Thus, higher altitude causes a generalized upward shift of the Hb and Hct distributions. This shift may be associated with the underdiagnosis of anemia for residents of higher altitudes when sealevel cutoffs are applied (CDC, unpublished data). Therefore, the proper diagnosis of anemia for those residing at higher altitudes requires an upward adjustment of Hb and Hct cutoffs. The values for altitude-specific adjustment of Hb and Hct are derived from data collected by the CDC Pediatric Nutrition Surveillance System on children residing at various altitudes in the mountain states (Table 3). Altitude affects Hb and Hct levels throughout pregnancy in a similar way (J. N. Chatfield, unpublished data).

The influence of cigarette smoking is similar to that of altitude, in that smoking increases Hb and Hct levels substantially. The higher Hb and Hct of smokers is a consequence of an increased carboxyhemoglobin from inhaling carbon monoxide during smoking. Because carboxyhemoglobin has

no oxygen carrying capacity, its presence causes a generalized upward shift of the Hb and Hct distribution curves (CDC, unpublished data). Therefore, a smoking-specific adjustment to the anemia cutoff is necessary for the proper diagnosis of anemia in smokers. The smoking-specific Hb and Hct adjustments are derived from the NHANES II data (Table 4).

The altitude and smoking adjustments are additive. For example, a woman living at 6000 feet and smoking two or more packs of cigarettes per day would have her cutoff for anemia adjusted upward by a total of 1.4 grams of Hb or 4% Hct.

Reported by: Div of Nutrition, Center for Chronic Disease Prevention and Health Promotion; Div of Environmental Health Laboratory Sciences, Center for Environmental Health and Injury Control; Div of Health Examination Statistics, National Center for Health Statistics; Div of Host Factors, Center for Infectious Diseases, CDC (MMWR vol 38, No. 22).

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Contribution of Birth Defects to Infant Mortality—United States, 1986

MMWR 1989:38:633-635

AS INFANT mortality in the United States has declined during the 20th century, the proportion of infant deaths attributed to birth defects has increased steadily (Figure 1). Birth defects also contribute substantially to years of potential life lost before age 65.2

To evaluate the contribution of birth defects to infant mortality in the United States, mortality data for 1986 from CDC's National Center for Health Statistics were analyzed. Birth defects were defined as conditions coded within Congenital Anomalies (740.0-759.9) of the International Classification of Diseases, Ninth Revision (ICD-9). Excluded from this group were 460 babies with lung hypoplasia (748.5), patent ductus arteriosus (747.0), or hydrocephalus (742.3) secondary to intraventricular hemorrhage (772.1) who also had ICD-9 codes 764 or 765 (disorders relating to low birthweight and short gestation).

Of 38,957 reported infant deaths in 1986, 8005 (20.5%) had birth defects listed as the underlying cause of death; birth defects were the leading cause of infant mortality (Figure 2). Birth defects were listed as a contributing

cause of death for an additional 1088 infants. Thus, in 1986 birth defects were an underlying or contributing cause of death for 9093 (23.3%) infants.

Cardiovascular defects, the most frequent type of birth defect, were present in 3057 (38.2%) of the 8005 babies. Central nervous system defects (including anencephalus and similar anomalies, spina bifida, and other congenital anomalies of the central nervous system and eye) were the second largest group, occurring in 1191 (14.9%). Birth defects of the respiratory system comprised the third largest group (870 [10.9%]). Reported by: Birth Defects and Genetics Br, Div of Birth Defects and Developmental Disabilities, Center for Environmental Health and Injury Control, CDC (MMWR vol 38, No. 37).

CDC Editorial Note: The rapid decline of infant mortality rates in the 1970s has been attributed largely to the advent of medical technology in the care of premature and other critically ill newborns. In the 1980s, this decline has slowed considerably—partly because of a lack of progress in primary prevention of conditions which lead to infant death. As a consequence, the 1990 health objective of nine infant deaths per 1000 live births

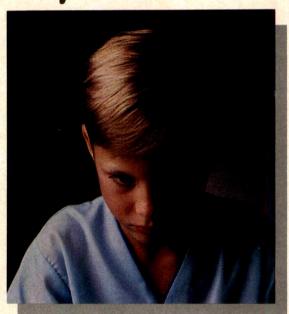
is unlikely to be met.³ Additionally, to meet the year 2000 objectives, health agencies will have to make substantial efforts to prevent the leading causes of infant mortality.

Birth defects, prematurity, and sudden infant death syndrome account for 52% of all infant deaths. Epidemiologic and basic research are integral to the development of prevention programs for infant mortality. The federal government and 22 states maintain surveillance systems for birth defects. These systems can assist in assessing the effectiveness of intervention programs in preventing defects whose etiology is known (e.g., fetal alcohol syndrome) and in serving as a basis for the epidemiologic research needed to understand the causes of birth defects.

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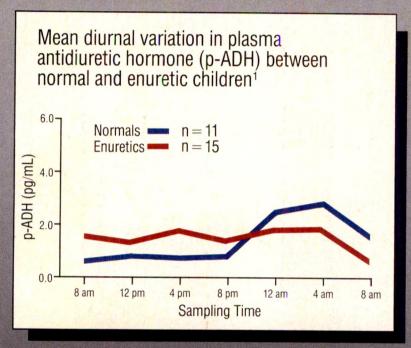
Landmark study now explains why Jimmy can't spend the night away from home



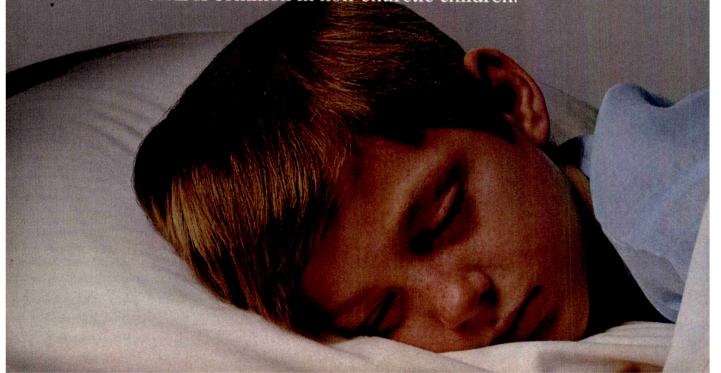
Jimmy is a bed wetter.

New study results indicate that he may have a physiologic problem.

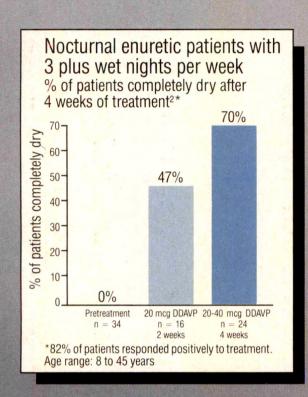
The ADH Deficit



Landmark study concludes: Enuretic children may lack diurnal rhythm of ADH common in non-enuretic children.¹



Announcing the first physiologic treatment for nocturnal enuresis



- DDAVP Nasal Spray, a synthetic analog of naturally occurring ADH, provides physiologic control of nighttime urine production in children 6 years of age or older¹⁻⁴
- Clinically proven in all degrees of nocturnal enuresis, even in many patients resistant to imipramine and alarms³
- Easy for children to use metereddose nasal spray administered at bedtime
- Outstanding safety record in patients of all ages⁵

DDAVP Nasal Spray

Safely Corrects the ADH Deficit

Please see next page for full prescribing information.



Safely Corrects the ADH Deficit

DDAVP Masal Spray Sig. 20-40 mcg intranasally at bedtime for nocturnal enuresis Disp. * 1 5.0 ml bottle

DESCRIPTION: DDAVP (desmopressin acetate) is an antidiuretic hormone affecting renal water conservation and a synthetic analogue of 8-arginine vasopressin. It is chemically defined as follows: Mol. wt. 1183.2

Mol. wt. 1183.2 Empirical formula: C.,H.,N.,O.,S., SCH,CH,CO-Tyr-Phe-Gin-Asn-Cys-Pro-D-Arg-Gly-NH, • C.,H.O., • 3H.O.

1-(3-mercaptopropionic acid)-8-D-arginine vasopressin monoacetate (salt) trihydrate.
DDAVP is provided as a sterile, aqueous solution for intranasal use. Each mL contains:
Desmopressin acetate.

to 40 IU.

1. The biphasic half-lives for DDAVP were 7.8 and 75.5 minutes for the fast and slow phases, compared with 2.5 and 14.5 minutes for lysine vasopressin, another form of the hormone used in this condition. As a result, DDAVP provides a prompt onset of antidiuretic action with a long duration after each administration. 2. The change in structure of arginine vasopressin to DDAVP has resulted in a decreased vasopressor action and decreased actions on visceral smooth muscle relative to the enhanced antidiuretic activity, so that clinically effective antidiuretic oser are usually below threshold levels for effects on vascular or visceral smooth muscle. 3. DDAVP administered intranasally has an antidiuretic effect about one-tenth that of an equivalent dissertion.

muscle. 3. DDAVP administered intranasally has an antidiuretic effect about one-tenth that of an equivalent dose administered by injection.

INDICATIONS AND USAGE:

Primary Nocturnal Enuresis: DDAVP is indicated for the management of primary nocturnal enuresis. It may be used alone or adjunctive to behavioral conditioning or other non-pharmacological intervention. It has been shown to be effective in some cases that are refractory to conventional therapies.

Central Cranial Diabetes Insigious: DDAVP is indicated as antidiuretic replacement therapy in the management of central cranial diabetes insigious and for management of the temporary polyuria and polydiosia following head trauma or surgery in the priutiary region. It is ineffective for the treatment of nephrogenic diabetes insigious. The use of DDAVP in patients with an established diagnosis will result in a reduction in urinary output with increase in urine osmolality and a decrease in plasma osmolality. This will allow the resumption of a more normal lifestyle with a decrease in urinary frequency and nocturia.

There are reports of an occasional change in response with time, usually greater than 6 months. Some patients may show a decreased responsiveness, others a shortened duration of effect. There is no evidence this effect is due to the development of binding antibodies but may be due to a local inactivation of the peptide Patients are selected for therapy by establishing the diagnosis by means of the water deprivation test, the hypertonic saline infusion test, and/or the response to antidiuretic hormone. Continued response to DDAVP can be monitored by urine volume and osmolality.

DDAVP is also available as a solution for injection when the intranasal route may be compromised. These situations include nasal congestion and blockage, nasal discharge, atrophy of nasal mucosa, and severe atrophic minitis. Intranasal delivery may also be inappropriate where there is an impaired level or consciousness. In addition, cranial surgical procedures, such as trans

trom surgery.

CONTRAINDICATION: Known hypersensitivity to DDAVP

WARNINGS: 1. For intranasal use only.

2. In very young and elderly patients in particular, fluid intake should be adjusted in order to decrease the potential occurrence of water intoxication and hyponatremia.

PRECAUTIONS:
General: DDAVP at high dosage has infrequently produced a slight elevation of blood pressure, which disappeared with a reduction in dosage. The drug should be used with caution in patients with coronary artery insufficiency and/or hypertensive cardiovascular disease because of possible rise in blood pressure.

Central Crania Diabetes Insipidus: Since DDAVP is used intransally, changes in the nasal mucosa such as scarring, edema, or other disease may cause erratic, unreliable absorption in which case intransasl DDAVP should not be used. For such situations, DDAVP injection should be considered.

Primary Noctumal Enuresis: If changes in the nasal mucosa have occurred, unreliable absorption may result. DDAVP intransasl solution should be discontinued until the nasal problems resolve.

Information for Patients: Patients should be informed that the bottle accurately delivers 50 doses of 10 mcg each. Any solution remaining after 50 doses should be discarded since the amount delivered thereafter may be substantially less than 10 mcg of drug. No attempts should be made to transfer remaining solution to another bottle. Patients should be instructed to read accompanying directions on use of the spray pump carefully before use.

carefully before use.

Laboratory Tests: Laboratory tests for following the patient with central cranial diabetes insipidus or postsurgical or head trauma-related polyuria and polydipsia include urine volume and osmolality in some cases
plasma osmolality may be required. For the healthy patient with primary nocturnal enuresis, serum electrolytes
should be checked at least once if therapy is continued beyond 7 days.

DRUG INTERACTIONS: Although the pressor activity of DDAVP is very low compared to the antidiuretic
activity, use of large doses of DDAVP with other pressor agents should only be done with careful patient
monitoring.

monitoring. Carcinogenesis, mutagenesis, impairment of fertility. Teratology studies in rats have shown no

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Teratology studies in rats have shown n abnormalities. No further information is available.
PREGNANCY—CATEGORY B: Reproduction studies performed in rats and rabbits with doses up to 12.5
times the human intranasal dose (i.e. about 125 times the total adult human dose given systemically) have
revealed no evidence of harm to the fetus due to desmopressin acetale. There are several publications of
management of diabetes insipidus in pregnant women with no harm to the fetus reported; however, no
controlled studies in pregnant women have been carried out. Published reports stress that, as opposed to
preparations containing the natural hormones, DDAVP (desmopressin acetate) in antidiuretic doses has no
uterotonic action, but the physician will have to weigh possible therapeutic advantages against possible
dangers in each individual case.

iterotonic action, but the physician will have to weigh possible therapeutic advantages against possible dangers in each individual case.
NURSING MOTHERS: There have been no controlled studies in nursing mothers. A single study in a postpartum woman demonstrated a marked change in plasma, but little if any change in assayable DDAVP in
breast milk following an intranasal dose of 10 mcg.
PEDIATRIC USE: Primary Nocturnal Enuresis: DDAVP has been used in childhood nocturnal enuresis. Shortterm (4-8 weeks) DDAVP administration has been shown to be safe and modestly effective in children aged
6 years or older with severe childhood nocturnal enuresis. Adequately controlled studies with intranasal
DDAVP in primary nocturnal enuresis have not been conducted beyond 4-8 weeks. The dose should be
individually adjusted to achieve the best results.

Central Cranial Diabetes Insipidus. DDAVP has been used in children with diabetes insipidus. Use in infants
and children will require careful fluid intake restriction to prevent possible hyponatremia and water intoxication.
The dose must be individually adjusted to the patient with attention in the very young to the danger of an

extreme decrease in plasma osmolality with resulting convulsions. Dose should start at 0.05 mL or less. Since the spray cannot deliver less than 0.1 mL (10 mcg), smaller doses should be administered using the nasal tube delivery system. Do not use the nasal spray in pediatric patients requiring less than 0.1 mL (10

mady per dose. There are reports of an occasional change in response with time, usually greater than 6 months. Some patients may show a decreased responsiveness, others a shortened duration of effect. There is no evidence this effect is due to the development of binding antibodies but may be due to a local inactivation of the peptide.

ADVERSE REACTIONS: Infrequently, high dosages have produced transient headache and nausea. Nasal congestion, rhinitis and flushing have also been reported occasionally along with mild abdominal cramps. These symptoms disappeared with reduction in dosage. Nosebleed, sore throat, cough and upper respiratory infections have also been reported.

infections have also been reported.

The following table lists the percent of patients having adverse experiences without regard to relationship to study drug from the pooled pivotal study data for nocturnal enuresis.

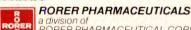
	PLACEBO (N=59)	20 mcg (N=60)	40 mcg (N=61)
ADVERSE REACTION	%	%	%
BODY AS A WHOLE	7	7	
Abdominal Pain	0	2	2
Asthenia	0	Ō	2
Chills	Ō	Ö	2
Headache	0	2 0 0 2	2 2 2 5 0
Throat Pain	2	Ō	0
NERVOUS SYSTEM			
Depression	2	0	0
Dizziness	0	0	3
RESPIRATORY SYSTEM			
Epistaxis	2	3	0
Nostril Pain	0	3 2 0 8	0
Respiratory Infection	2	0	0
Rhinitis	2	8	3
CARDIOVASCULAR SYSTEM			
Vasodilation	2	0	0
DIGESTIVE SYSTEM			
Gastrointestinal Disorder	0	2 0	0
Nausea	0	0	2
SKIN & APPENDAGES			
Leg Rash	2 2	0	0
Rash	2	0	0
SPECIAL SENSES			
Conjunctivitis	0	2 2	0
Edema Eyes	0	2	0
Lachrymation Disorder	0		2

Edema Eyes

Lachnymation Disorder

OVERDOSAGE: See adverse reactions above. In case of overdosage, the dose should be reduced, frequency of administration decreased, or the drug withdrawn according to the severity of the condition. There is no known specific antidote for DDAVP. An oral LD_{sc} has not been established. An intravenous dose of 2 mg/kg in mice demonstrated no effect.

DOSAGE AND ADMINISTRATION: Primary Nocturnal Enuresis: Dosage should be adjusted according to the individual. The recommended initial dose for those 6 years of age and older is 20 mcg or 0.2 mL solution intransasily at bedtime. Adjustment up to 40 mcg is suggested if the patient does not respond. Some patients may respond to 10 mcg and adjustment to that lower dose may be done if the patient has shown a response to 20 mcg. It is recommended that one-half of the dose be administered per nostril. Adequately controlled studies with intransasil DDAVP in primary nocturnal enuresis have not been conducted beyond 4-8 weeks. Central Cranial Diabetes Insipidus: DDAVP dosage must be determined for each individual patient and adjusted according to the diurnal patient or response. Response should be estimated by two parameters: adequate duration of sleep and adequate, not excessive, water turnover. Patients with nasal congestion and blockage have often responded well to DDAVP. The usual dosage range in adults is 0.1 to 0.4 mL daily, either as a single dose or divided into two or three doses. Most adults require 0.2 mL daily in two divided doses. The morning and evening doses should be separately adjusted for an adequate diurnal rhythm of water turnover. For children aged 3 months to 12 years, the usual dosage range in adults is 0.1 to 0.3 mL daily, either as a single dose or divided into two odses. About 1/4 to 1/3 of patients can be controlled by a single daily dose. The morning and evening doses should be separately adjusted for an adequate diurnal rhythm of water turnover. For children aged 3 months to 12 years, the usual dosage range in 0.0 t



RORER PHARMACEUTICAL CORPORATION Fort Washington, PA. U.S.A. 19034

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Editorial

Agent B

Genetics and Litogens

I wrote about agent A in August 1987. Agent A is a substance contained in a common household retail product. A pregnant woman used this product and gave birth to a son with microcephaly with subsequent mental retardation. A lawsuit was initiated on behalf of this child. The allegation was that agent A had crossed the placenta and injured his brain. This allegation was denied by the company that compounded the product containing agent A.

Agent A had never been found to damage infants during fetal development, and on independent medical examination the child was found to have an autosomal recessive form of microcephaly.²⁻⁴ Both parents carried the gene for microcephaly and each of their offspring had a one-fourth risk of having microcephaly. Therefore, agent A had nothing to do with the child's condition.

The outcome of lawsuits can be surprising, and juries can be unpredictable. The plaintiff in the case of agent A was a child. A jury might see him as the victim of an uncaring company and make an unjustified award. To prevent this possibility, the case of agent A was settled out of court for a large sum. The child's lawyer shared in this award.

A postscript can now be added; the company that made the retail product had maintained that it was blameless, but they now have become a plaintiff. They sued the company that manufactured and supplied agent A for incorporation into their retail product. They alleged that agent A was teratogenic, an allegation they had just denied. The company argued this point using the same expert witnesses for the child whose testimony they had previously refuted.

At the time I wrote about agent A, I had consulted on "over 100 legal cases." Since then I have consulted on another 100 cases. Several have in-

volved agent B. Agent B is important to pediatricians and family physicians caring for children. To administer agent B is good pediatric practice.

The lawsuits involving agent B are all alike. The allegation is that agent B has injured the child's brain. The suit is directed against the child's physician and the company that makes agent B. My role in such cases has been to determine whether genetic or other prenatal factors may have caused the child's condition. One patient will serve to illustrate the litigation surrounding agent B.

A boy had received agent B and subsequently developed seizures; he is mentally retarded. I reviewed the medical records on the child and his immediate family members. The records were largely in another language and extracting the relevant information was difficult. At least two of his siblings are also retarded. None of the children in this family had been fully evaluated as to cause.

The family in this case of agent B lived far away; it required a full day of air travel to reach them. Two of my colleagues traveled to see the family and returned with a preliminary description and laboratory specimens. The retarded children in the family, according to my colleagues, looked and behaved alike. For example, they all had large, prominent ears, were unusually shy, and avoided eye contact; yet they were inappropriately loquacious and jocular.

All of the blood and urine specimen test results were negative, except for the cytogenetic analysis. The plaintiff had the fragile X chromosome. His lymphocytes showed gaps in the chromosome band Xq27.3 induced by exposure of the cells to medium free of folate and thymidine or to methotrexate or fluorodeoxyuridine, accepted methods for inducing the cytogenetic expression of the fragile X chromosome.⁵ The retarded siblings, a

brother and a sister, also had the fragile X chromosome.

Children with the fragile X chromosome tend to have subtle, but characteristic, physical and behavioral features. Large, prominent ears are part of the physical phenotype. Shyness, avoidance of eye contact, inappropriate loquaciousness, and jocular effect are part of the behavioral phenotype.

The allegations in this case involving agent B are twofold. One is that the child became mentally retarded as a result of an adverse reaction to the administration of agent B. The second allegation is that agent B caused the child to develop a seizure disorder. Let us look at each of these allegations.

Mental retardation is perhaps the best known feature of the fragile X chromosome phenotype. The fragile X chromosome is second only to Down syndrome as a chromosomal cause of mental retardation. Since Down syndrome is usually due to sporadic trisomy 21, the fragile X chromosome is the most common familial type of chromosome anomaly in mental retardation.5-8 About 80% of males and 30% to 50% of females with the fragile X are mentally rechromosome tarded. 5,9-12 Thus, the mental retardation in the plaintiff can be expected with the fragile X chromosome and so it can be attributed to this chromosome abnormality without reference to agent B.

The seizure disorder is the second type of damage allegedly due to agent B. The first report of the marker X chromosome, now known as the fragile X chromosome, was in 1969 by Lubs. ¹³ In this original study, Lubs found seizures.

Seizures have been frequently reported in males with the fragile X chromosome since that time. 14-18 For example, Nielsen 17 found seizures in 4 of 27 males with the fragile X chromosome, for a frequency of 15%. For

another example, I recently saw a family with 2 boys who had the fragile X chromosome. One of the affected boys had had seizures, whereas there was no other family history of seizure disorders.

There can be no doubt that mental retardation and seizures occur in males with the fragile X chromosome and are part of the fragile X syndrome. Mental retardation is present in 80% of affected males, 5,9-12 as mentioned above, and of them, perhaps 15% or more 5,12-18 have seizure disorders.

The logical conclusion is that the association with agent B is spurious and the legal action should be dismissed. Is another sizeable settlement in the offing? Will a jury find in favor of the plaintiff and dole out a large amount of money?

After the appearance of the agent A story,¹ I received a number of letters. One was from Frank A. Disney, MD, of the Elmwood Pediatric Group in Rochester, NY. He wrote that he had experience in seven legal cases—"three that were settled when they should not have been, one settled when it should have been, one in progress that should be settled, one found for the defendant, and one found for the plaintiff for a small facial scar that should not have been paid, but what jury is going to reject payment to a pretty blond teenager?"

There is almost a wildly random unpredictability to court decisions in medicolegal cases today. Juries tend to be at sea, swamped by conflicting opinions and by facts they cannot fathom. Judges may also be uninformed about the endless intricacies of science and medicine.

Robert A. Mendelson, MD, a pediatrician in Portland, Ore, assumed I would "outline what changes" should be made in the legal system "and how they might be implemented." One change I would suggest is that judges, unless they possess an adequate knowledge of the relevant science and medicine, be required to appoint and use an expert panel. I would far rather be appointed by the judge as an expert than be employed by the defense or plaintiff counsel. Other expert witnesses whom I know would

also prefer to be placed in this neutral position.

The recommendation that judges in such cases appoint and use an expert panel is neither new nor revolutionary. Judges currently have the authority to appoint experts to advise the court. However, this authority is only infrequently exercised today by judges. Of the 200 cases on which I have consulted, all involved highly sophisticated and very complex biomedical matters. In none of these cases, to my knowledge, has a judge appointed an expert panel to counsel the court. To do so would presumably be to admit a lack of complete breadth and depth of expertise by the judge in biomedical

The quotation in the front of *The Malformed Infant and Child* by Goodman and Gorlin¹⁹ is from Maimonides, the 12th century philosopher and physician. The quotation is: "Teach thy tongue to say I do not know." This admonition applies to everyone, including judges and us. The greatest ignorance is *not* to say "I do not know."

Agent B, like agent A, is a litogen. Litogens are agents or events that differ from teratogens, mutagens, and carcinogens in that litogens do not cause congenital malformations, mutations, or cancer but do cause lawsuits.

Agent B is an essential part of the practice of pediatrics. Hence, the case of agent B touches everyone concerned with child care. I have also met attorneys who do nothing except defend the companies that make agent B against lawsuits.

This is a major issue not only for the law but also for pediatrics and parents. Among the possible future scenarios, one is frightening and the other is entrancing. The frightening scenario is that the manufacturers of agent B abandon it due to the liability and cost of legal defense.

Without the availability of agent B, lawsuits concerning its use will cease, but they will soon begin again because children will needlessly become sick, and some will die. The entrancing scenario is that the legal system will recognize this very real danger and act to bar or penalize frivolous suits in this area. Perhaps it is too much to

hope that the law really cares for the health of our children.

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The Editorial Board Speaks . . .

Alan D. Bedrick, MD





Alan joined our editorial board as Associate Editor in 1988 and has remained on the board after our move to Tulane University. He received his medical education at Penn State University in Hershey, completed his residency at the University of Arizona, and continued with a fellowship in neonatology at State University of New York-Health Science Center in Syracuse. He joined the faculty at the University of Arizona in 1983 and was promoted to associate professor with tenure in 1989.

Alan has received many awards dating back to his undergraduate days; the most recent was a commendation from the College of Medicine for his outstanding contribution to medical education. Alan is a neonatologist with interest in gastrointestinal physiology and development in young animals and in premature infants. He has been supported with local and National Institutes of Health grants in pursuing his investigations of the role of prostaglandins in the developing intestine. Alan is also an excellent clinician and is repeatedly cited for his excellence in student and resident education.

He has been a faithful and diligent editorial board member with critical but fair judgment. He currently edits the department, "Pediatric Perspectives."

Neonatology in Residency Curricula: How Much Is Too Much?

Rarely does a week go by when a faculty member or pediatric resident of my department does not make a slightly underhanded comment concerning the amount of time house staff spend on neonatal intensive care unit (NICU) rotations. The range of critiques is quite wide but most often focuses on why residents spend so much time caring for patients whose weight in grams is often in three digits, and whose disease processes are few in number and are usually known by their three letter abbreviations (RDS, BPD, NEC, PDA, etc). I am regularly asked why residents spend apparently inordinate amounts of time (both in daytime "required" rotations and night call) in the NICU when the great majority of house staff will not provide this type of care once they complete residency training.

I believe that the overwhelming majority of neonatologists involved in postgraduate medical education realize that their goal is not to turn pediatric residents into junior neonatologists. We must accept the fact that some years ago, considerable time was allocated to the NICU in pediatric residency curricula to meet patient care and service demands, in addition to educational requirements. However, it is not appropriate for residents to spend 6 months (or more) on NICU rotations. Much of the work performed by residents in NICUs can be accomplished by other qualified health care professionals, such as neonatal nurse practitioners. (However, keep in mind that with constraints of a looming "80-hour work week" resulting in limitations on available house staff hours and manpower, neonatal nurse practitioners will work half as many hours per week as residents for more than twice as much money!)

Perhaps the essence and importance of neonatology rotations lies in the wide exposure to basic pediatric medicine and the experience and approach to problem-solving in the critically ill patient. For example, the basic concepts and management approach to pediatric fluid and electrolyte disturbances can be learned just as well on a 1000-g patient as a 10-kg patient. (Just be careful with the decimal points!) The same can be said for treatment of suspected infection, resuscita-

tion, and many other fundamentals of pediatric medicine. In addition to the calculator "number-crunching" common to NICU resident "work rounds" (calculation of daily fluid intake and output, joules per kilogram per day, etc), there is an aspect of the neonatology rotation that cannot be quantitated. It is often the NICU in which interns first experience the death of a patient. The impact of a patient's death on health care providers is independent of the patient's size and weight. There is much to be said for the intangible education residents obtain in the nursery when caring for the family of a dying infant.

Although house staff become quite skilled and proficient at ventilator management and writing orders for parenteral alimentation, this is not the primary goal of the rotation. Residents learn an approach to the critically ill patient—not just by organ system, but to the patient as a whole. Although neonatologists may care for many patients with respiratory disorders, we must not lose our vision that we are truly "generalists" for the newborn. We care for infants with disorders of every organ system (and carefully consider recommendations from subspecialty consultants who may not see the "forest" because of their particular interest only in a certain "tree").

If this sounds like a soapbox diatribe from a somewhat paranoid individual trying to justify his existence, then let that be the case. General pediatricians need significant experience in the NICU. Although they may not provide NICU tertiary care once in practice, many will be involved in neonatal resuscitation and stabilization, and nearly all will care for infants discharged from the NICU. As biomedical technology improves and smaller infants survive, there will be more infants with ongoing medical problems requiring sophisticated pediatric care after discharge from the nursery. Pediatricians must have an in-depth understanding of the origins, initial treatments, and ongoing management of these problems. There is much more to the NICU than three-digit weights and three-letter words.

Increased Airway Leukotriene Levels in Infants With Severe Bronchopulmonary Dysplasia

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 The sulphidopeptide leukotrienes (C4, D4, and E4) are potent airway constrictors that have been detected in the airways of infants with pulmonary hypertension and viral infections. The present study was undertaken to test the hypothesis that leukotrienes in tracheal lavage fluid are elevated in bronchopulmonary dysplasia. Twenty-six intubated infants (10 with bronchopulmonary dysplasia, 9 with hyaline membrane disease, and 7 normal controls) had tracheal lavage leukotriene levels determined by radioimmunoassay. Lavage fluid cell counts (alveolar macrophages) and leukotriene levels were significantly increased in infants with severe bronchopulmonary dysplasia. The increased concentration of leukotrienes seen in the infants with bronchopulmonary dysplasia would suggest a possible role for these compounds in the pathophysiology of this disease.

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A rachidonic acid oxidative metabolism through the 5-lipoxygenase pathway produces a group of biologically active compounds known as leukotrienes. Leukotrienes C4, D4, and E4 (sulphidopeptide leukotrienes) are potent airway constrictors.1 Previous reports have suggested that leukotrienes may be involved in the pathogenesis of adult respiratory distress syndrome in pediatric patients,2 bronchoconstriction during acute viral infections,3 and bronchopulmonary dysplasia (BPD) in neonates.4 The present study was undertaken to test the hypothesis that sulphidopeptide leukotrienes in tracheal lavage fluid are elevated in BPD. Two additional groups of infants were studied for comparison: (1) premature neonates with hyaline membrane disease (HMD), and (2) a group of normal infants, age matched to the patients with BPD.

PATIENTS AND METHODS

This study was reviewed and approved by the Institutional Review Board of the University of Tennessee, Memphis. The study population consisted of 26 infants in three groups: (1) 10 infants with HMD who were studied within the first 48 hours of life, (2) 9 infants in whom severe bronchopulmonary dysplasia developed after prolonged ventilation for HMD, and (3) 7 normal infants, age matched to the group with BPD, who underwent general anesthesia for hernia repair. All infants were intubated and receiving assisted ventilation when the lavage sample was taken.

Tracheal lavage samples were obtained at the time of routine suctioning for pulmonary toilet in the following manner. One to two milliliters of normal saline solution was placed down the endotracheal tube followed by 5 to 10 breaths, which were provided by either the infant's respirator at the previous setting or manually by the anesthesiologist. A sterile suction catheter then was inserted to at least the level of the carina, and the lavage fluid (0.5 to 1 mL) was collected in a sterile plastic mucous trap. Sample volumes were measured, the fluid was centrifuged, and the supernatant was frozen immediately at -60°C for later radioimmunoassay of leukotrienes. Cell counts were done in a hemocytometer, and the cells were identified using Wright's stain under light microscopy.

Leukotrienes were measured using antibodies, tracer, and standards from Advanced Magnetics, Inc (Cambridge, Mass). The leukotriene antibody binds to sulphidopeptide leukotrienes (LTC₄, LTD₄, LTE₄, and LTF₄) but not to LTB₄ or prostanoids tested (prostaglandins F₂ and F_{2a}, thromboxane B₂, 6-keto-prostaglandin F_{1a}). Assays were performed in phosphate buffer. After

24 hours of incubation at 4°C, the free fraction was separated from that bound to antibody by absorbing the unbound ligand on activated charcoal. Data were handled by computer with determination of second-order regression of tracer bound to antibody against unlabeled leukotriene by the method of least squares. All unknowns were assayed at two dilutions, and the unknown dilution curves and the standard curve had to be parallel before the results were accepted. Values are reported in picograms per milliliter with a lower limit of detection of 100 pg/mL.

Statistical comparisons among the groups were done using a one-way analysis of variance and a post hoc Scheffé's test with a significance level of P = .05.

RESULTS

The Table summarizes the results from this study. The infants with HMD were studied within the first 2 days of life, whereas the mean age of the group with BPD was 81.2 ± 11.2 days and of the normal group, 85 ± 15 days. The two patient groups were similar in gestational age and birth weight, while the normal group was born at term. Ventilation values were much higher in the group with BPD at the time of study, but the respirator setting during the first 48 hours of life for the group with BPD was similar to that of the group with HMD (peak inspiratory pressure, 19±3 mm Hg; inspired oxygen, 38% ± 5%). Lavage fluid cell counts were much higher in the group with BPD. The predominant cell type in the group with HMD was mature polymorphonuclear leukocytes (0.82), while the group with BPD had a predominance (0.92) of alveolar macrophages.

Leukotriene levels are also given in the Table; the group with BPD had a significantly higher leukotriene concentration than the other groups of infants. Leukotriene levels in the normal group were nondetectable.

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Clinical and Laboratory Results*					
	HMD (n=10)	BPD (n=9)	Normal (n = 7)		
GA, wk	28.9 ± 0.7	29.5 ± 1.5	38.5 ± 1.3†		
BW, g	1106±95	1258 ± 120	2980 ± 308†		
Age at study, d	1.5±0.2	81.2 ± 11.2†	85 ± 15†		
PIP, cm H₂O	18±2	42±5†			
Inspired O ₂ , %	40 ± 6	85±8†			
WBC count, ×103/mL	112±60	875 ± 206†	<100/mL		
LT, pg/mL	163±45	2792 ± 209†			

*HMD indicates hyaline membrane disease; BPD, bronchopulmonary dysplasia; GA, gestational age; BW, birth weight; PIP, peak inspiratory pressure; WBC, white blood cell; and LT, leukotrienes. Values are mean ± SEM.

†P<.05 vs group with HMD.

COMMENT

The present study reports a significant increase in leukotriene levels in the tracheal lavage fluid of neonates with BPD compared with infants with HMD and age-matched infants with normal lungs. Also, there was an increase in alveolar macrophages in infants with BPD, which has been shown to be an important part of the generalized lung damage in this disease. ^{5,6}

Leukotrienes are known to be potent

constrictors of airways¹ and may contribute to the increased pulmonary vascular resistance seen in neonatal pulmonary hypertension.¹ The origin of tracheal fluid leukotrienes is probably the increased number of leukocytes seen in the fluid. Although fetal and adult lung tissue are capable of leukotriene production, the amount produced is minimal, and airways produce mainly LTA₄.¹ Tracheal tissue does not appear to be able to convert LTA₄ to the sulphi-

dopeptide leukotrienes.⁸ Lung epithelial cells, neutrophils, eosinophils, and alveolar macrophages are all capable of synthesizing sulphidopeptide leukotrienes.^{1,9}

Increased airway resistance is present in infants with BPD, ¹⁰ and it has been reported that compounds that inhibit leukotriene release, such as cromolyn sodium, may help to decrease airway resistance. ¹¹ The increased concentration of leukotrienes seen in our infants with BPD suggests that these compounds could be involved in the bronchospasm associated with BPD. Further study on the functional significance of leukotrienes in the airways of infants with BPD may help to uncover a possible therapeutic role of leukotriene antagonists.

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Effects of Unrestricted Diet on Mild Infantile Diarrhea

A Practice-Based Study

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· Dietary restriction in cases of mild infantile diarrhea is often advocated but has not been shown to be effective. We enrolled 176 healthy infants less than 1 year of age in a randomized controlled trial to determine the effects of diet on the course of mild diarrhea. When diarrhea occurred (56 episodes), infants were randomly assigned to a treatment diet (24 hours of electrolyte solution then dilute sov formula, dilute cow's milk formula, or undiluted soy formula) or their usual formula. Parents recorded daily weights, stool losses, and oral intake. The difference in effects of unrestricted and treatment diets was small and not clinically significant. Patients on an unrestricted diet averaged 0.7 fewer days of diarrhea (95% confidence interval [CI], -1.43 to 0.02), 5.0 fewer total stools (95% CI, -10.26 to 0.33), and 1% less weight loss (95% CI, 2% to -1%) compared with those receiving a treatment diet. Treatment fallures were similar in both groups. An unrestricted diet does not appear to affect the course or symptoms of mild diarrhea.

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The initial treatment of mild acute diarrhea remains controversial. Dietary manipulation is a popular approach to therapy among practicing pediatricians. A recent survey of US pediatricians, for example, showed that more than 50% recommend ingestion of clear fluids until the second or third day of acute diarrhea.1 Recent recommendations from authoritative organizations, however, have tended to deemphasize the importance of dietary restriction. 2,3 The World Health Organization recommends continuation of an infant's regular feeding during diarrhea, and the American Academy of Pediatrics recommends no more than a 24-hour

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delay in the reintroduction of feeding. The Academy does recommend that formula feeding "should be reintroduced gradually by starting with dilute mixtures."

Recent studies suggest that the early reintroduction of full feeding after rehydration leads to better outcomes, 45 but no information is available about appropriate dietary changes at the onset of diarrhea. We conducted a controlled trial of unrestricted diet vs dietary manipulation in infants with mild acute diarrhea.

PATIENTS AND METHODS

The study was conducted between September 1985 and April 1985 at two suburban pediatric practices in Rochester, NY. To identify patients at a uniform point in their illness, we enrolled healthy infants without diarrhea. Healthy patients who were brought to the office for their 2- or 4-month well-child examinations during the study period were asked to participate in the study. Although all patients were not approached if the office was extremely busy or if the physician thought the parents could not comply with the study requirements.

Parents of 176 patients agreed to participate in the study. At the time of enrollment, we provided each family with spring-loaded home baby scales and supplies of the infant's usual formula, soy formula, and oral electrolyte solution.

We instructed parents to contact the office by telephone if diarrhea occurred. If, at the time of the telephone call, the patient had had two or more watery stools in 24 hours, or three times the usual number of stools in 24 hours, the infant was entered into the study protocol. Episodes of diarrhea that occurred while infants were taking antibiotics were excluded from the trial. No cases of diarrhea were too severe for inclusion.

Infants with diarrhea were randomly assigned in a 2:1 randomization to a treatment or control group. Randomization was by episode of diarrhea, so that repeated episodes of diarrhea in individual patients were each randomized.

The management of infants in the treatment group reflected what we thought were dietary manipulations commonly prescribed by pediatricians. All the patients in the treatment group received oral electrolyte solution for 24 hours. Following this initial period, patients were randomly assigned to one of three regimens: (1) one-quarter-strength soy formula advanced in one-quarter-strength increments daily; (2) full-strength soy formula; or (3) one-quarter-strength cow's milk formula advanced in one-quarter-strength increments daily.

Infants who usually ate soy formula could be assigned only to a soy formula: those who ate cow's milk formula could be assigned to either soy or cow's milk formula. This difference in assignments was necessary because we thought that switching from sov to cow's milk formula would be unacceptable to parents accustomed to feeding soy formula. Patients in the control group continued their usual formula or breast-feeding without adding clear fluids other than those usually taken. We instructed families of infants in both treatment and control groups to discontinue solid foods during the episode of diarrhea. Dilute formulas were prepared by mixing formula with the electrolyte solution.

We instructed parents to weigh their child twice a day during the episode of diarrhea and to record the number, size, and character of stools, as well as the volume and type of feeding consumed. Parents were contacted daily by telephone throughout the duration of the illness to ensure that measurements were taken. Patients were seen in the office at the discretion of their pediatrician, but no changes were made in the dietary regimens at such visits unless a treatment failure was confirmed.

We defined treatment failure as a weight loss of more than 4% of the previous day's weight or the occurrence of more than twice the number of stools since the previous day. Infants who met the criteria for treatment failure were given 24 hours of oral electrolyte solution, then returned to dilute or full-strength formula or breast milk. We defined the duration of diarrhea as the number of days until the last semiliquid stool. Treatment failures were excluded from the calculation of other outcome measures.

We used analysis of variance (ANOVA) to compare differences between treatment groups for outcome variables. Bonferroni's adjustment for multiple comparison was used when performing stratified analysis of subgroups. Multivariable regression analysis was used to examine the effect of compliance on outcome. The Wilcoxon Rank Sum Test was used to test for the effect of nonnormal distribution on ANOVA results. Fisher's Exact Test was used for categorical data, and 95% confidence intervals were calculated for the differences in effects of treatment and control diets. 6,7 The study was approved by the Committee on Investigations Involving Human Subjects at the University of Rochester School of Medicine.

RESULTS

Although we initially hoped to analyze the effects of the different dietary treatments, the number of patients was insufficient to do so. Therefore, we compared patients assigned to any treatment diet with those who continued to receive their usual formula.

A total of 63 episodes of diarrhea occurred in 59 infants during the study period. Seven episodes were excluded from analysis: 6 families failed to perform home measurements and 1 refused randomization. Thus, a total of 56 episodes of diarrhea were analyzed.

Twenty-one episodes of diarrhea were assigned to the control group and 35 to the treatment group. The baseline characteristics of infants in the treatment and control groups were similar (Table 1). The mean age (\pm SE) of patients was 7.0 ± 2.1 months in the treatment group and 6.8 ± 2.3 months in the control group. Thirty-eight percent (8/21) of control patients were 6 months of age or younger, while 23% (8/35) of treatment patients were 6 months or younger.

The differences in outcomes for the infants in the treatment and control groups were small and neither clinically nor statistically significant (Table 2). For four of five outcomes, differences favored the control (unrestricted) diet. Treatment failures were similar in both groups, and all cases resolved without prolonged diarrhea or hospitalization.

To determine whether the failure to observe a difference between treatment and control groups was due to the effects of one of the dietary treatments, we stratified the outcomes of the treatment and control groups by the type of feeding. No significant differences were evident in outcomes among any of the treatment or control subgroups (ANOVA P>.003 for 15 comparisons, Bonferroni's adjustment for multiple comparisons). The number of patients was too small in each stratum, however, to detect anything but large differences between subgroups.

A marked difference in compliance occurred between the treatment and control groups. All infants randomized to an unrestricted diet were compliant. They remained on their usual diet and were not given solid foods, and new clear fluids were not added. In contrast, among patients randomized to a treat-

ment diet, 30% were given formula that was not prescribed or were given solid foods (P<.005). The parents of these infants often complained that their infants did not have their hunger satisfied by the oral electrolyte solution and dilute formula. There was no change in outcome, however, when patients who were not fully compliant were removed from the analysis.

We also compared energy and fluid intakes in the treatment and control groups. Treatment patients consumed a significantly greater volume of fluid during the first 4 days of the study. These results were consistent with par-

ents' subjective observations that infants given dilute formula were hungrier. Energy intake was similar in each group. This occurred because infants in the treatment group consumed a greater volume of fluid (Table 3). Patients given the control diet had a greater energy intake only on the second day of treatment (P=.0005). This increased energy intake occurred while patients in the treatment group were still consuming dilute formula.

COMMENT

This study demonstrates that dietary manipulation does not affect the outcome of mild diarrhea as seen in general

	Control (N=21)	Treatment (N = 35) No. (%)	
Characteristic	No. (%)		
Male	10 (48)	17 (48)	
Fever	4 (19)	6 (17)	
Vomiting	2 (10)	8 (23)	
Usual diet Cow's milk formula	8 (38)	20 (57)	
Soy formula	9 (43)	15 (43)	
Breast milk	4 (19)	0	

Table 2.—Outcome of Dietary Treatment of Mild Diarrhea in Infants*							
Variable	Control Group (N=21)	Treatment Group (N = 35)	Difference (Control – Treatment)	95% Confidence Interval of Difference			
Duration of diarrhea, d	3.8	4.5	-0.7	-1.43, 0.02			
Weight change during illness, %	0.0	-1.0	+1.0	+2, -1.0			
Total No. of stools/ illness	10.7	15.7	-5.0	10.26, 0.33			
No. of stools/d	2.6	3.5	-0.9	-1.88, 0.12			
Treatment failures, %	9.5	8.6	1.1	15, + 17			

^{*}Treatment consisted of 24 hours of clear fluid followed by random assignment to dilute cow's milk or soy formula. Control infants had no dietary changes. Numbers indicate mean values.

Table 3.—Fluid and Energy Intake for Control and Treatment groups by Day of Illness in Mild Diarrhea

	D	aily Fluid I	ntake, mL/k	g	Da	ily Energy	intake, kJ/k	g
	Control Group			Treatment Control Group Group			Treati Gro	
Day	Mean	SE	Mean	SE	Mean	SE	Mean	SE
1	65.5	10.4	116.5	11.3*	183.1	29.8	202.0	19.7
2	122.5	10.8	157.8	10.7*	311.2	23.5*	202.9	17.2
3	99.2	10.0	149.4	7.9*	274.3	27.7	236.0	19.7
4	95.7	8.3	138.2	11.7*	260.8	23.1	277.2	19.3
5	94.6	11.26	136.0	16.7	257.5	27.7	274.7	15.5
6	85.9	27.24	150.3	22.7	215.0	49.6	341.5	53.8

^{*}P<.05.

pediatric practice in the United States. Patients who were fed their usual formula tended to have fewer stools, less weight loss, and a shorter duration of illness. In contrast, infants given a restricted diet appeared to be hungrier, and their parents were less likely to comply with instructions.

Although infants in the control group had a better outcome than those in the treatment group, the difference was not statistically significant. The confidence intervals are narrow enough to exclude any clinically significant benefit of treatment, however.8 For example, the duration of diarrhea in control patients could have been as much as 1.4 days less than in treatment patients. In contrast, patients in the treatment group had little chance of having diarrhea lasting 0.02 day less than control patients. Thus, we believe that these data support the view that altering infants' formulas has no clinically significant benefit on the outcome of diarrhea.

An important finding of this study was the marked degree of noncompliance among families in the treatment group. This degree of noncompliance surprised us. Previous studies in our pediatric practices have resulted in greater than 90% compliance. Furthermore, noncompliance occurred despite daily telephone contact to encourage parents to give the treatment as prescribed.

Our results are consistent with others that demonstrate that early return to full-strength formula following rehydration is associated with greater weight gain, without prolongation of illness.4,5,11 For example, in the study by Santosham et al⁵ of Apache Indians admitted to the hospital for oral rehydration, infants who were returned immediately to full-strength soy formula after rehydration had decreased stool output compared with infants whose formula was gradually increased in strength. Unlike previously studied patients, however, ours were not ill for several days prior to therapy. Therefore, we could assess the immediate effects of dietary changes.

Several studies have found an association between the reintroduction of formula and worsened diarrhea. 12-16 All of these studies, however, were performed on infants referred to tertiary centers, including some infants who

were malnourished or severely ill. These results are not applicable to patients commonly seen in the outpatient setting because such patients represent quite a different spectrum of illness than that found in a general pediatric practice.

This study and studies of hospitalized infants differ in regard to the questions that each type of study can address. When hospitalized patients are studied, questions of the efficacy of treatments under ideal conditions may be addressed because it is possible to control all aspects of the patients' care. Such studies probably overestimate the benefits of therapy when they are applied to outpatients, however, because they cannot account for compliance. The use of outpatients allowed us to explore the effectiveness of dietary restriction under usual circumstances.

Our data do not permit us to comment on the role of cow's milk formula in the outcome of diarrhea. Although lactose malabsorption has been found in association with diarrheal disease, its importance among outpatients in developed countries has been studied only by Groothius et al17; they found that lactose malabsorption was not associated with worse outcome. Indeed, the importance of diet in determining the severity of diarrhea has not been well studied. 4,18 It is possible that other factors, such as the cause and severity of infection, are more important than diet in determining the outcome of diarrhea.

We have shown that restricting diet to clear liquid for 24 hours followed by a gradual reintroduction of formula is no more effective than continuing regular feedings throughout episodes of acute mild diarrhea. Furthermore, recommendations to restrict infants' diets are associated with clinically important noncompliance, which suggests that future investigations of the treatment of diarrhea should address parents' concerns and priorities in addition to determining which therapies are most effective.

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Clavicular Fractures in Neonates

Paul R. Joseph, MD, Warren Rosenfeld, MD

 We evaluated the wide variation in the reported incidence of fractured clavicles (0.2% to 3.5%) in newborns by screening 626 consecutive infants delivered vaginally for fractures. One of us (P.R.J.) evaluated all infants, twice during the initial hospital stay and 2 weeks later. Eighteen fractured clavicles were identified for a frequency of 2.9% (18/626). One fracture was discovered on the first hospital examination, 10 on discharge, and 7 at follow-up. Only 2 patients had symptoms usually associated with fractured clavicles. The most reliable clinical sign for inhospital diagnosis was difficulty in feeling the margins of the affected clavicle when compared with the normal clavicle. The mean birth weight of the infants was 3604 g (range, 3000 to 4930 g), and no obstetric complications occurred. The reported frequency of fractures diagnosed clinically during hospitalization significantly underestimates their occurrence. Most newborn infants with fractures have no symptoms and minimal physical findings during the first days of life, making repeated examination necessary.

(AJDC. 1990;144:165-167)

A lthough the clavicle is the most frequently fractured bone in the neonate, 18 the true frequency has been inadequately documented. The studies of Farkas and Levine and Enzler performed 40 years ago probably provide the most accurate information on the frequency of clavicular fractures in the newborn population. They reported a frequency for fractured clavicles of 1.7% and 2.6% determined by roentgenographic examination in 300 and 500 consecutive infants delivered vaginally. In addition, Farkas and Levine re-

ported that in the next 655 vertex deliveries following their roentgenographic study, only one fractured clavicle was detected by clinical examination in the hospital (0.2%).

In our clinical experience, diagnosis of clavicular fractures in the hospital is often difficult. We noted clavicular callus formation in two asymptomatic infants who had normal findings on physical examinations in the hospital shortly after birth. These findings stimulated us to evaluate prospectively the frequency and presentation of clavicular fractures in our population of newborn infants.

PATIENTS AND METHODS

All newborn infants examined by the senior author (P.R.J.) were carefully evaluated for findings of clavicular fracture on admission to the nursery, on discharge from the hospital, and at the first office visit (14 to 28 days later). The examiner attempted to identify swelling or tenderness over the clavicle, crepitation, pain on pressure, and lack of movement of the arm. Special attention was given to the examination of the clavicles during this time. With the infants completely uncovered and lying on their backs, the examiner (standing at the foot of the crib) gently felt the right clavicle with the second and third fingers of his left hand, and he felt the left clavicle with the second and third fingers of his right hand. He compared the right and left clavicles with regard to the ease with which the borders of the clavicles could be defined. He also compared the pressure necessary to feel the right clavicle with the pressure necessary to feel the left clavicle. If any significant difference was suspected or detected in infants examined in a hospital, clavicular roentgenograms (except in patients 16 and 17; Table 1) were obtained. The senior author examined infants in four hospitals. In one hospital, all neonates were also examined by a pediatric resident.

During a 32-month period, 597 full-term newborn infants delivered vaginally were examined by one of us (P.R.J.) in the hospital and at the first visit at 2 weeks of age. An

additional 29 patients, delivered at hospitals where the senior author was not on the medical staff, were seen at 2 weeks of age.

If patients were still in the hospital and a clavicular fracture was suspected (patients 1 through 14 between November 1985 and December 1987), roentgenographic examination was performed to confirm clavicular fracture. Between January and June 1988, the diagnosis of clavicular fracture was established in 2 infants without roentgenographic confirmation; in both, the fracture was confirmed by the presence of callus at the first office visit. If the fracture was diagnosed during the first office visit by the finding of a large swelling over the clavicle, no roentgenographic examination was performed.

RESULTS

From the cohort of 626 vaginal deliveries, 18 fractured clavicles were diagnosed (frequency of 2.9%) (Table 1). Only 2 infants (patients 5 and 12) had signs and symptoms on initial examination. Patient 5 was irritable and cried when handled or moved and did not move his right arm. Patient 12 had a bruised and cool right arm. The diagnosis of clavicular fracture was not established until the examination at discharge. Nine additional fractures were diagnosed at the time of discharge. In these patients, only minimal swelling over the clavicle was noted. Nine of the 11 fractures suspected clinically during hospitalization were confirmed roentgenographically. Seven fractures were identified at the time of the first office visit because of the presence of a large callus over one clavicle. All 11 patients diagnosed in the hospital also had callus formation noted at the first office visit.

The mean birth weight of the patients with fractures was 3604 g (range, 3000 to 4930 g); the female-male ratio was 13:5. Thirteen of 18 fractures were on the right side. There was only one complicated delivery (difficult second stage)

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Table 1.—Clavicular Fractures in Newborn Infants When Patient Weight, Affected No. of Apgar Roentgenographic kg Diagnosed* **Previous Births** No./Sex Side Comments Examination 1/F 3.9 Office visit , L 2 8/9 2/F 3.4 L Office visit 3 8/9 No R 3/M 3.6 H2 9/10 Yes R 4/F 3.0 Office visit 8/9 No R H1 5/M 3.8 9/10 Not moving R arm 2 Yes 6/F 3.5 R Office visit · 8/10 No 7/F R Office visit 0 9/10 3.5 No 8/F 3.9 Ħ ; H2 1 9/10 Yes 9/M 3.2 R Office visit : 0 9/10 No 4.9 R H2 10/F 0 7/9 Yes 11/F 3.8 L H2 Difficult delivery, 0 9/10 second stage 2.5 h 12/F 3.5 R H2 Bruised R arm 8/10 Yes Petechiae on .13/F 3.4 R H2 n 9/10 Yes face, neck 14/F 3.2 H2 10/10 Yes 3.2 Office visit 10/10 15/F No H2 2 16/M 3.9 8/9 No 17/F R H2 9/10 3.3 0 No R 0

H2

18/M

3.8

Method		Author, y	Ý	Location	No. of Deliveries	No. (%) of Clavicular Fractures
Roentgenography of		Farkas and Levine, 1950		Baltimore, Md	300 -	5 (1.7)
consecutive newborns		Enzler, ⁵ 1950	•	Switzerland	500	13 (2.6)
Single examiner, office follow-up		Present study	:	Long Island, NY	626	18 (2.9)
Single examiner, no		Muus, ⁷ 1903		Denmark :	`1600 <u>.</u>	22 (1.4)
office follow-up		Troitzkaja, 1926		USSR	2222	32 (1.4)
•		Hukewytsch, 1929	•	USSR	2213	32 (1.4)
•	2	Hedberg, 1946	;	Sweden .	. 2450	87 (3.5)
•		Enzler, ⁵ 1950		Switzerland	5630	105 (1.9)
		Nasso and Verga,11 1954		Italy	3574	81 (2.3)
Multiple examiners, no	ş	Madsen, 1955	1	Denmark _x .	105119	726 (0.7)
office follow-up	ing.	Farkas and Levine, 1950		Baltimore, Md	665	1 (0.2)
· ·	1	Rubin,12 1964		Philadelphia, Pa	15 435	43 (0.3)
•		Levine et al, 13 1984		Cincinnati, Ohio	13870	28 (0.2)
	; ;	Present study		Long Island, NY	11 078	د 58 (0.5)

and all Appar scores were 8/9 or better, except for 1 patient who had a 7/9 Apgar score. The neonates had been delivered by 13 obstetricians at six different hospitals. None of the obstetricians informed the pediatrician of problems during delivery or of feeling or hearing a crack of a bone at the time of delivery, which is their customary practice if this does occur.

COMMENT

Symptoms of clavicular fracture, as described in basic pediatric and neonatal texts, include irritability and crying during spontaneous or passive motion of the arms. 1-3 Signs of clavicular fractures include instability, motion, or crepitations at the fracture site; significant local swelling; and asymmetric Moro reflexes. Only 1 of the 18 patients in our study had any of these signs or symptoms. The most common abnormal physical finding in our series was minimal swelling or fullness over the fracture site. The presence of a normal clavicle with which to compare the fractured clavicle made diagnosis possible; most of the fractures diagnosed in the hospital might have been missed had no com-

9/10

Yes

^{*}H2 indicates second hospital examination; H1, first hospital examination.

parison been possible. On the affected side, bony margins of the clavicle could not be felt as easily as on the unaffected side. This sign was most helpful during the examination at discharge but not at the initial physical examination.

It has been suggested⁶ that missed clavicular fractures in newborn infants are greenstick fractures, while the more easily diagnosed fractures are complete fractures. This was not our experience. Only one greenstick fracture (in patient 18) was found in our series. The roentgenogram was interpreted as probable artifact, although a fracture could not be ruled out. On the first office visit, the child was asymptomatic but had a large callus over the right clavicle.

The mothers' number of previous live births or the infants' Apgar scores did not appear to correlate with the presence of newborn clavicular fractures. While the average and median weights of the infants were approximately 3600 g, a little above average size, the infants with clavicular fractures were certainly not excessively large infants. It is not clear why most clavicular fractures were on the right or why most infants involved were female.

Information on the frequency of clavicular fractures in the literature (Table 2) is derived primarily from hospital studies without office follow-up. The frequency varies from 0.2% to 3.5%, 10 though recent reports 6,12,13 suggest a frequency of 0.2% to 0.7% for full-term newborns. The reports by Farkas and Levine⁴ and Enzler⁵ are of particular interest because they are the only stud-

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ies in which routine roentgenograms of the clavicle were performed for a group of newborn infants. Farkas and Levine roentgenographically examined 300 consecutive infants who had been delivered vaginally with use of low forceps. Five complete clavicular fractures (frequency of 1.7%) were diagnosed. None of these five infants had any symptoms. and the infants all had normal findings on initial examinations in the nursery. Enzler obtained roentgenograms in 500 consecutive infants delivered vaginally in Switzerland and found 13 fractures (frequency 2.6%). In the 626 infants delivered vaginally and examined by one of us (P.R.J.) over a 32-month period, the frequency of clavicular fractures was 2.9% (18/626). We also confirmed the observations of Farkas and Levine and Enzler on the infrequency of signs and symptoms in the newborn with a clavicular fracture and the frequency of clavicular fractures after normal, nontraumatic vaginal deliveries.

Our observed frequency of 2.9% should be of particular interest to hospital administrators, to chiefs of departments of obstetrics and pediatrics, and to hospital quality assurance committees, since New York State (and undoubtedly other states) now requires that all clavicular fractures in newborns be reported to the State Health Department. To be more accurate as an indicator of the quality of care, the reporting of newborn clavicular fractures might be limited to a frequency greater than 3% for any one hospital or practice.

To estimate the previously recognized diagnoses of clavicular fracture in

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our community, we reviewed the charts of all newborns with this discharge diagnosis in 1985 and 1986 in three of four community hospitals. Fifty-eight clavicular fractures were diagnosed among 11 078 infants delivered vaginally, for a frequency of 0.5%, approximately one sixth of that reported in our series. This figure of 0.5% was similar to that reported in studies based on physical examinations in the hospital and by multiple examiners (Table 2). The frequency of fractures diagnosed in the hospital in the present study was 1.8% and rose to 2.9% when diagnoses made at the first office visit were included. This rate was similar to that noted in studies in which roentgenographic studies were performed on consecutive deliveries. The data from Table 2 suggest that the diagnosis of clavicular fractures in newborns is increased by a combination of skill, interest, and time of the examining physician and by reexamination in an office follow-up visit 2 weeks later. The trend toward early discharge of newborn infants mandates careful follow-up examination if fractures of the clavicle are to be identified.

The present study supports the hypothesis that newborn clavicular fractures have occurred throughout the Western world over the past 85 years with a fairly stable frequency ranging from 1.5% to 3.5%. Our series suggests that 80% of newborns with clavicular fractures have no symptoms and have minimal physical findings on examination during the first few days of life.

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Capillary Blood Gases in the Neonate

A Reassessment and Review of the Literature

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• Heel puncture capillary blood gas (CBG) measurements continue to be used in neonates for estimating arterial blood gas values. Review of the literature reveals general agreement that CBG Po, values are of little use in predicting arterial Po, and that CBG pH values are reliable predictors of arterial pH; opinion varies regarding CBG Pco., We conducted a twopart study comparing postductal arterial and CBG values. First, 50 infants were studied, each only once. All infants had umbilical arterial catheters in place. Blood was obtained simultaneously from the umbilical artery catheter and the warmed heels. Results demonstrated poor predictability of arterial values from CBG pH and Pco2 as well as for Po2. Second, to determine if variation both within and among individuals was similar, repeated measurements were made in 27 additional infants comparable to the first group. We obtained 3 to 28 simultaneous postductal arterial and CBG samples from each infant. A random-effects nested analysis of variance indicated that for pH, variation was largely the result of between-subject or within-subject replicates effects, while for Po, and Pco, most variation was explained by differences between the two techniques (umbilical artery catheter vs CBG). The results indicate that CBG measuréments do not accurately predict arterial values in neonates. Extreme caution should be used when management decisions are based on CBG values.

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Despite the availability of arterial lines, transcutaneous (tc) monitoring, and pulse oximetry, capillary blood gas (CBG) measurements continue to be

me caution ment deci-

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Reprint requests to Division of Newborn Medicine, Children's Medical Center, One Children's Plaza, Dayton, OH 45404 (Dr Courtney). used in some intensive care nurseries to estimate arterial pH, Pco,, and Po,. In our nursery, marked differences of opinion as to the predictive value of CBG measurements stimulated us to review the literature on this topic. The diversity of methods and differing results among studies reported to date led us to reassess CBG values in two prospective studies in our neonatal intensive care unit population. The first was designed to assess the degree of agreement between arterial blood gas (ABG) and CBG values in postductal samples. The second was designed to examine the sources of variation between ABG and CBG results: within-subject variation (replicates effect), ABG vs CBG values, and random errors. Institutional review board approval was obtained for both studies, and signed, informed parental consent was obtained from one or both parents prior to study.

SUBJECTS AND METHODS Study 1

Fifty infants were studied, each only once. Thirty-one were males and 19 were females; their gestational ages, by Ballard examination, ranged from 25 to 44 weeks (mean, 33 weeks), their age at study ranged from 1 to 25 days (mean, 7 days), and their weight at study ranged from 580 to 4630 g (mean, 1954 g). All infants had umbilical artery catheters (UACs) in place and were normotensive for their age and weight. All infants demonstrated good peripheral perfusion and absence of peripheral edema.

Postductal capillary samples were ob-

Pco₂, mm Hg

Po₂, mm Hg

tained from both heels to assess two methods of warming the extremities. A water bath was heated to 43°C. A plastic-lined diaper was soaked with heated water and wrapped around one foot for 5 minutes. The other foot was immersed in a cup of the heated water for the 5-minute period.

Infants were studied while they were resting quietly. A nurse withdrew 3 to 5 mL of blood to clear the UAC, obtained the sample, and flushed the UAC as the study technician obtained the CBG samples. The same study technician drew all CBG samples from all infants. The method recommended by Blumenfeld et al¹ was used to obtain capillary blood, using the most medial or lateral portions of the plantar surface of the heel, without squeezing the heel to augment the blood flow.

Arterial blood samples were obtained by withdrawing 0.2 mL of blood into a heparinized 1-mL syringe after withdrawing 3 to 5 mL of blood to clear the line; capillary samples were obtained by completely filling a standard heparinized capillary tube. For both studies all samples were evaluated immediately on the same blood gas analyzer (model 178, Corning Instruments, Corning, NY); the CBG samples were evaluated first, followed by the UAC samples.

Study 2

Repeated measurements were made in 27 infants similar to those in study 1 to quantify the sources of variation for the differences between CBG and ABG values. Infants were normotensive and nonedematous and had UACs in place. Heel-stick blood was arterialized using a diaper soaked in water heated to 43°C and left in place for 5 minutes. Arterial and capillary blood samples were obtained at

Table 1.—Mean ± SEM Values in Study 1					
	Capillary	Blood Gas			
Arterial Blood Gas	Wrapped	Immersed			
7.38 ± 0.01	7.40 ± 0.01	7.41 ± 0.01			
40.8 ± 1.1	39.5 ± 1.0	38.3 ± 1.1			
765+23	523+14.	50.7 + 1.5			

precisely the same time. Ten female and 17 male infants ranging from 27 to 41 weeks' gestation by Ballard examination (mean, 34 weeks) were studied. The age at first sampling ranged from 1 to 27 days (mean, 4 days), and weight at first sampling ranged from 760 to 3340 g (mean, 2087 g). Infants were studied no more than twice daily until removal of their UAC. Samples were obtained simultaneously with routine blood glucose estimations to eliminate the need for extra heel punctures. From 3 to 28 samples per infant were obtained (mean, 8 samples).

RESULTS Study 1

Analysis of variance demonstrated no effect of sex, gestational age, age, or weight at testing on the differences between ABG and CBG values, except for a small positive correlation of age at testing with pH in the CBG samples obtained by immersion of the heel in water (the older the infant, the higher the pH in these CBG samples). Since this difference was not found in CBG samples obtained by wrapping the heel, it is interpreted as a chance finding. There were no significant differences between the values obtained using the two methods of warming the heel prior to obtaining samples. Mean values for the three sampling methods are shown in Table 1. Correlations and regressions between ABG and CBG values are shown in Figs 1 through 3. Correlations were best for pH, intermediate for Pco, and worst for Po.

Though CBG values were correlated with ABG values, SEs of the regression equation predicting arterial values from capillary values were large. For pH CBG measurements with the heel wrapped, r = .80; however, the SE = .04; assuming a capillary pH of 7.40, this means, from the 95% confidence levels, that the arterial pH could vary from 7.32 to 7.48. Similarly, a capillary PCO2 of 40 mm Hg could correspond to an arterial PCO2 of 30 to 50 mm Hg, and a capillary Po2 of 60 mm Hg could correspond to an arterial Po₂ of 90 mm Hg. No capillary value was higher than the arterial value for Po..

Prediction of any one arterial value from any one capillary value would be even more inaccurate, since the confidence interval for the mean of a sample always involves a smaller SE than do intervals related to prediction of single values. Also, the SE gets even larger as

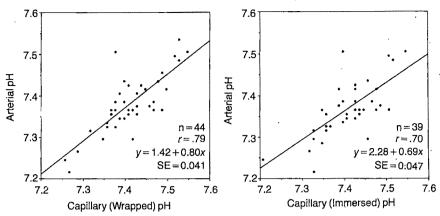


Fig 1.—Arterial blood gas pH values compared with pH values from capillary blood gas samples obtained with the heel wrapped (left) or immersed (right).

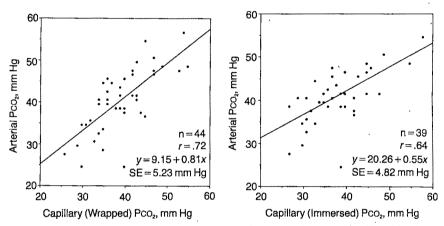


Fig 2.—Arterial blood gas PCO_2 values compared with PCO_2 values from capillary blood gas samples obtained with the heel wrapped (left) or immersed (right).

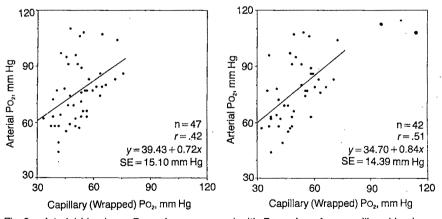


Fig 3.—Arterial blood gas PO₂ values compared with PO₂ values from capillary blood gas samples obtained with the heel wrapped (left) or immersed (right).

the single values move away from the mean.

The mean ± SE base excess, as calculated from a standard nomogram, ^{2(p+1/8)}

was -1.1 ± 0.5 mmol/L for the ABG samples, 0.6 ± 0.5 mmol/L for the CBG samples obtained by wrapping the heel, and 0.1 ± 0.6 mmol/L for the CBG sam-

ples obtained by immersing the heel in hot water. Base excess differences between ABG and CBG samples were statistically significant, with mean arterial values 1.5 ± 0.3 mmol/L lower than mean CBG values (both wrapped and immersed, P<.0001).

Study 2

The 219 paired samples from the 27 infants were analyzed using analysis of variance of repeated measurements. Every measurement is subject to variation. This variation may be due to biological differences between individuals, differences due to measurements on the same individual at different times, random variation, or differences in the measurements themselves (ABG vs.)

CEG). The analysis of variance of repeated measurements was performed to investigate the differences between AEG and CBG values after other sources of variation were accounted for. Results are summarized in Table 2 and indicate that for pH, variation is largely the result of differences between sub-

jects (63% of the total variation) or over repeated measures (time) in the same subject (30% of the total variation). For PCO₂ and PO₂, 60% and 98% of the tota variation, respectively, is explained by the differences between arterial and capillary methods. Longitudinal assessment in the same infant does not im

Table 2.—Proportion of Total Variation in Study 2
Proportion of Total Variation,

•	Proportion of Total Variation, %				
	рН	Pco₂	Po ₂		
Between subjects	63.0 ·	31.0	1.6		
Within subjects Repeated measurements	30.0	7.0	0.4		
Arterial blood gas vs capillary blood gas	2.0	60.0	97.7		
Random error	5.0	2.0	0.2		

sampling, 1 heel

was warmed. 1 was not

	Measure- ments Made		ents Made No. o		No. of Paired	Sample Sites					
Source, y	pН	Pco ₂	Po ₂	No. of Patients		Population	Capillary	Arterial	Methcds	Results	
Thomsen, ³ 1964	Yes	Yes	No	Not stated	16 pH, 14 Pco₂	Premature infants	Not stated	Temporal artery stick	Simultaneous sampling	Poor correlation for both pH and Pco.	
Gandy et al,4 1964	Yes	Yes	No	106	149	66 healthy, 40 ill infants ≤2 wk old, ≥2000 g	Heel	UAC or femoral artery stick	Samples taken within 5 min of each othe.; 23 capillary samples were unwarmed	Good correlation for pH and Pco ₂ in healthy infants >3 h old; pcorer correlation in sick infants >3 h old; very poor correlation if capillary samples were unwarmed	
MacRae and Palavradji,⁵ 1966	Yes	Yes	No	18	112	14 term, 4 preterm infants	Heel	UAC	Timing not spec- ified	Difference was not clinically significant	
Desai et al, ^e 1967	Yes	Yes	Yes	Not stated	2424 pH, 14 Pco ₂ , 25 Po ₂	Infants with tetanus receiving curare, age unspecified	Scalp	Temporal artery stick	Ethyl chloride spray for capillary samples, timing not specified	Good correlation for pH, Pco ₂ , and Po ₂	
Koch and Wendel, ⁷ . 1967	Yes	Yes	Yes	36	61 [°]	Term, healthy infants	Heel	UAC	Simultaneous sampling	Poor correlation of pH and Pco₂ in infants <24 h old, better correlation in infants >48 h old; very poor correlation for Po₂ at all ages	
Banister, ⁶ 1969	Yes	Yes	Yes	13	45	Infants with respiratory distress syndrome 3-95 h old	Heel	UAC	Capillary samples first	Good correlation for pH, poor correlation for Po₂ and Pco₂	
Usher,º 1969	Yes	Yes	Yes	Not stated	"About 200"	Distressed infants	Heel	UAC	Simultaneous sampling	Good correlation for pH, not good for Pco₂; reliable correlation for capillary Po₂ values ≤65 mm Hg	
Corbet, ¹⁰ 1970	No	No	Yes	36	60	3 normal infants, most were sick	Finger	Radial or temporal artery stick	Arterial sample was drawn f rst, no warming, samples were drawn within 10 min of each other	"Generally close" agreement for Po₂	
Mountain and	Yes	Yes	Yes	- 62	47 ill,	47 ill,	Heel	UAC	Simultaneous	Poor correlation for Po ₂	

Table 3.-Review of the Literature*

15

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healthy

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Campbell,11

1970

prove the accuracy of results, as each infant may change with time and such changes cannot be precisely assessed.

COMMENT

The literature regarding comparisons of CBG and ABG values in newborn infants is summarized in Table 3. It is difficult to compare many of these studies. In some, samples were not obtained simultaneously, making interpretation difficult, 48,10,16,16 Many studies used multiple paired samples per patient, which may have biased the results. 4,57,8,10,12,13,15-17,19 Though heel vs UAC values were most commonly assessed, other sites were used by some au-

thors. ^{3,6,10,15,16} Ages, weights, and degrees of illness varied considerably among studies. Some authors showed plotted correlations without r values, making interpretation difficult: ^{3,4,6-8,12,15} Standard deviations or SEs were sometimes not given¹⁴; in such cases it is possible that good correlations exist, but wide scatter limits clinical usefulness. Methods other than warming for arterialization of the capillary sample were also employed. ^{6,12-14}

Taken as a group, most previous studies have found capillary pH values to correlate well with arterial values, with only three studies reporting poor correlations at various ages or degrees of

illness. ^{8,4,7} For PCO₂, about half the reported studies found good correlations for capillary and arterial samples; the other half did not. For PO₂, almost all studies reported poor correlations; only three studies found little discrepancy, ^{6,10,16} although several studies noted closer correlations at low PO₂ values. ^{9,18,14,17}

Given the wide variations in methodology and technique as well as the incompleteness of information concerning design and results in some studies, it is difficult to assess why some investigators find good correlations and others do not.

Arterial lines, to monitors, and pulse

Measure- ments Made				No. of Paired	2	Sample Sites				
Source, y	рН	Pco ₂	Po2		Samples	Population	Capillary	Arterial	Methods	Results
Winquist and Stamm,¹² 1970	Yes	Yes	Yes	35	46	1 d to 14 y old	Heel or finger	UAC or brachial artery stick	Simultaneous sampling, iontophoresis for capillary samples	Close correlation for pH and Pco ₂ , Po ₂ prediction was accurate if infant was ≥5 d old
Glasgow et al, 13 1972	Yes	Yes	Yes	26 .	53	Sick infants 10 h to 2 wk old	Heel .	UAC	Simultaneous sampling, vasodilating cream for capillary samples	Close correlation for pH and Pco ₂ ; poor correlation for Po ₂ if capillar result was >60 mm Hg, good correlation if result was <60 mm Hg
Hunt,1 1973	Yes	Yes	Yes	44	37 pH, 37 Pco ₂ , 41 Po ₂	3.5 d to 10 wk old	Heel ,	Indwelling line :	Simultaneous sampling, histamine iotophoresis in one heel, no arterialization in the other heel	Close correlation for pH, capillary Pco ₂ values were 10-15 mm Hg higher than arterial values, Po ₂ correlation was reliable if Pao ₂ <60 mm Hg
Duc and Cumarasamy,¹⁵ 1974	No	No	Yes	13	40 '.	III infants 1-3 wk old	Finger	UAC	Methods of Corbet ¹⁰	Poor correlation for Po ₂
Karra and Poland, ¹⁶ 1978	Yes	Yes	Yes	33 ,	70	Ill infants, age not specified	R hand	Temporal or R radial artery stick	Capillary samples were obtained first	Good correlation for pH, Pco ₂ , and Po ₂
Folger et al, ¹⁷ 1980	Yes	Yes	Yes .	59	76	III infants <5 d old, 900- 3600 g	Heel	UAC	Simultaneous sampling	Good correlation for pH and Pco ₂ ; poor correlation for Po ₂ unless capillary Po ₂ was <40 mm Hg
Lewis and Haslam,18 1984	No	Νo	Yes	6	Not stated	III infants	Heel	UAC	Simultaneous sampling	Poor correlation for Po ₂
McLain et al,¹º 1988	Yes	Yes	Yes	41	158	Preterm infants	Heel	UAC	Simultaneous sampling	Satisfactory correlations for pH and Pco ₂ capillary values; unsatisfactory correlation for Po ₂
Present report								•		
Study 1	Yes	Yes	Yes	50	50	Nonedematous, normotensive ill infants 1-25 d old	Heel .	UAC .	Arterial sample preceded capillary sample by a few seconds	Capillary values poorly predicted arterial values for pH, Pco ₂ , and Po ₂
Study 2	Yes	Yes	Yes	e 27	219	Nonedematous, normotensive ill infants, longitudinal assessment	Heel	UAC .	Precisely simultaneous sampling	Capillary values poorly predicted arterial values for pH, Pco ₂ , and Po ₂

^{*}UAC indicates umbilical artery catheter.

oximeters have become standard items in intensive care nurseries. Nonetheless, arterial lines are not without risk, 20 and many neonatologists prefer to remove them as soon as possible. Transcutaneous monitors are often in short supply in busy nurseries. Tissue perfusion and skin edema affect the correlation with ABG values, 21 and skin damage may occur. 22 Though some monitors provide tcPco, as well as tcPo, values, there is not as yet a way to noninvasively monitor pH. Pulse oximetry, a valuable adjunct to oxygen monitoring in the newborn, 23,24 does not assist in monitoring PCO, or pH. Thus, when an arterial line is not in place, CBG values continue to be obtained and used for clinical monitoring and management decisions. The availability of te monitoring has, however, allowed observation of the fluctuations that can occur in tcPo, and tcPco. values during capillary blood collection. Graham and Kenny²⁵ reported unpredictably increased or decreased tcPo, values during capillary sampling in 30 premature infants. They concluded that inappropriate management could result from reliance on CBG Po2 values, because of the significant and unpredictable deviations that can occur compared with the resting state. Kost et al26 reported similar findings for tcPCO₂ during capillary sampling and concluded that reliance on capillary PCO₂ values for management decisions was inappropriate, even if CBG values accurately predicted arterial values at the time they were obtained.

Capillary blood gas values appear to be more accurate in adults than in infants.²⁷ Whether better correlation exists for the older infant needs to be assessed in future studies. In our unit, as in others, the older infant with bronchopulmonary dysplasia is frequently the most common subject for CBG assessment. Arterial lines have long been removed from these infants, and to values are often unreliable.^{28,29}

Our studies suggest that basing management decisions on CBG values obtained during the neonatal period is potentially a problem. Capillary pH and PCO₂ as well as PO₂ are subject to wide variation from ABG values. Though study 2 samples were obtained at precisely the same moment, study 1 capillary samples lagged a few seconds behind arterial samples, since two capillary samples were obtained, one from each heel. Results can thus be interpreted as representing a change in the infant's state; ie, ABG values obtained

precisely simultaneously with both CBG values would have been closer to the capillary values. Since the ABG samples were drawn with the infant in a quiet, resting state, and given the findings of Graham and Kenny²⁵ and Kost et al,²⁶ this interpretation does not affect the validity of our findings. Though capillary values for base excess were slightly higher than arterial values, this is not likely to be clinically relevant, and CBG values may be of use for this determination. MacRae and Palavradji,⁵ Koch and Wendel,⁷ and Hunt¹⁴ drew similar conclusions from their work.

We conclude from our studies that CBG values are, at best, only gross predictors of arterial values and, at worst, misleading assessments that may result in inappropriate management decisions. Extreme caution must be used when CBG samples are obtained. All available information, including to readings, oxygen saturation, and clinical status of the infant, must be assessed, and important management decisions should be based on ABG samples drawn from indwelling arterial lines whenever possible.

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Special Contribution

Trends and Implications of Women in Pediatrics

Michael S. Kappy, MD, PhD, Catherine DeAngelis, MD

It is in changing that things find purpose.
HERACLITUS

There has been a marked increase in the number of women in the labor force generally since 1950, when only 18% of women with children worked outside the home and only 12% of women in the work force had preschool-age children. By 1988 these figures had increased to 66% and 57%, respectively. The fastest-growing segment has been women with children less than 1 year of age. In 1950 only 22% of families had two wage earners, whereas the figure for 1988 was 62%. The reasons for this change include a decrease in the average effective male wage by approximately 25% over the last 15 years and the growing necessity for women in the work force to preserve the middle-class status to which many families have become accustomed.

The types of jobs for women are largely unchanged, with the No. 1 occupation being secretary, followed by elementary school teacher, bookkeeper, cashier, and office clerk, all of which account for 75% of women in the work force. However, in 1960, only 5.5% of MD degrees were held by women, but by 1975 the figure had increased to 13%, by 1985 to 30%, and by 1987 to 36%. Similar trends have occurred in dentistry, where the percentage of women receiving DDS degrees increased from 3%

in 1975 to 21% in 1985. In law, 15% of degrees were earned by women in 1975 compared with 38% in 1985.

Dr Brownlee quoted a survey of firsttime registrants showing that the percentage of American women registering to take the pediatric board examination increased from 24% in 1974 to 50% of all registrants in 1987. The figure is anticipated to have been greater than 50% in 1988. For foreign medical graduates, the figure rose from 43% to 60% between 1974 and 1983, but it dropped to 45% in 1987. Overall, the percentage of female registrants was 30% in 1974 and 51% in 1988. Women in subspecialties showed differing patterns of change. The percentage of women in cardiology remained constant or decreased slightly from 1979 to 1987, but this was accompanied by increases in endocrinology, hematology/oncology, and neonatology. Increased numbers of women are also expected to enter pulmonology and critical care over the next several years.

Women make up half the population from which future physicians should be chosen. Furthermore, women who choose medicine show some distinct, important differences from men. Dr Harvey reported on a survey of 605 women physicians from all specialities in Illinois in 1986, showing that of those entering pediatrics, the two top motivating factors were working with children and the emotional challenge. The two lowest factors were income and prestige. At the same time, a survey of 180 freshman medical students at the University of Wisconsin in Milwaukee showed that 62% of women compared with only 28% of men rated patient contact highly in their list of career priorities. A total of 41% of women vs 22% of men rated family life as an important consideration, and 30% of women vs 16% of men ranked the number of hours worked highly.

The average salary of American women in general is approximately 65% that of their male counterparts, viz, \$17 000 vs \$26 000. Eighty percent of women who work full time earn \$20 000 or less yearly. Only one third of the difference between wages is attributable to seniority or experience. This discrepancy in salaries is also found in the medical profession.

Although increased numbers of women are graduating from medical schools, a significant discrepancy remains in the ranks of women in academia. Women are generally older at the time of promotion, possibly because they are meeting family responsibilities, and only 30% of them have ranks above assistant professor compared with 58% of men. The bottleneck is not at the level of promotion and tenure committees but in the initial recommendation from chairmen. The discrepancy is also found at many administrative levels; for example, there is only one woman on the American Board of Pediatrics Executive Committee. Also, many if not most university medical schools have only male department heads. It is imperative to address the important issues of discrimination in academic rank and inequity in salaries before serious consequences occur. Such discrepancies discourage bright young women from choosing medical careers.

IMPLICATIONS FOR TRAINING PROGRAMS

Some major factors influencing residency training programs include marital status, pregnancy and delivery, and obligations to spouse and children. Dr

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Trends and Implications of Women in Pediatrics was the third annual conference on issues in pediatric education held under the auspices of St Joseph's Hospiral and Medical Center, Phoenix, Ariz; it was conducted from October 21 through 23, 1988, in Scottsdale, Ariz.

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Harvey presented data from a 1986 American Academy of Pediatrics survey of self-designated pediatricians from the American Medical Association master files showing that only 4% of board-certified male pediatricians were single compared with 14% of board-certified female pediatricians. Female physicians were more often married to other physicians than were male physicians, probably due to the restricted social life that female physicians have during training and because many men with less education than them are reluctant to become seriously involved.

The percentage of female pediatricians who were divorced was twice that of men. Approximately 20% of spouses of board-certified men worked full time. whereas 93% of board-certified female pediatricians had full-time working spouses. The female pediatricians tended to marry at the same rate as other women but at an older average age, and they had fewer children.

In another survey of 904 women physicians less than 50 years of age, 64% had children, and 85% of these women had their first child between the ages of 26 to 34 years, at a mean age of 29 years. This is considerably older than the mean age for the general population. Of the women who had children, 43% had them while still in their residencies. However, 67% trained in programs with no maternity leave policy. Of the 33% who trained in programs that did have a maternity leave policy, two thirds had 6 weeks or less and 84% had 12 weeks or less of official maternity leave. Less than one sixth of women reported that training programs were helpful in the care of their infants after they returned to work. In another study, 14 of 22 specialty boards surveyed had no maternity leave policy but left this up to the discretion of individual training program directors.2 The specialty boards and residency review committees cannot define maternity leave policies, since their primary responsibility is education. They can only define the total time required in training or experience; however, the Pediatric Board requires that a candidate have 33 months of training in an accredited program. This has led to some program directors allowing pregnant residents (and those of any gender with serious

illness or problems) to use elective time for scholarly activity, such as writing case reports, reviews of the literature, results of research, and so forth.

The responsibilities of child and home care go beyond the pregnancy period. A study by the American Academy of Pediatrics' showed that 6% to 12% of married male pediatricians reported that they were responsible for housework compared with more than 50% of married female pediatricians. Seventy-six percent of the married men compared with only 6% of the married women had spouses who were primarily responsible for housework. None of the married male pediatricians reported that they were primarily responsible for the care of children younger than 6 years, whereas 6% of women reported that they were. The remainder had help in the house or had arranged for day care. Only a small percentage of men in this study were responsible for child care for children older than 6 years, whereas 28% of the married female pediatricians were responsible.

The pediatric program directors must assure that the primary purpose of residency training is education. On the other hand, the clinical services need to be provided by competent persons. However, the bottom line is that education must be complemented by the service, or the service has no place in the training program. Compromises must be available to accommodate absences for maternity leave as they are for sick leave or other absences. From the other perspective, residents, when possible, should try to time their pregnancies to allow the least disruption to the program.

How does one best cover for maternity leave? Is sharing a residency position between two persons a practical solution? Is trading electives and using them for scholarly reading and writing a reasonable solution?

The ability of a training program to be flexible with maternity leave depends at least to some degree on the program size. Furthermore, if women take extensive maternity leave, there are practical difficulties for them in carrying their time over into new academic years as far as scheduling and funding are concerned. Shared or 4-year residencies require careful planning, but they might solve many of the problems of pregnancv and child care.

From the institutional standpoint, a balance between departments is needed for maternity leave policy. At several institutions, 1 month's maternity leave can be taken as an elective in addition to vacation time.

Harassment from supervisors regarding not getting pregnant should not be tolerated. On the other hand, differential treatment, for example, asking single residents or those with no children always to take holiday call, is also not fair. Furthermore, it can lead to very negative feelings regarding child rearing during residencies.

There is a great need for a broad counseling policy for men and women in residency programs so that problems arising from outside responsibilities, such as the family, may be addressed prospectively.

The stress for women in residencies is often compounded by family moves; ie, male spouses move for their careers, yet they often are unwilling to accompany their pediatrician wives if they must move. This probably contributes to the increased divorce rate among female pediatricians.

Do women contribute to programs differently than men? Many participants felt that women generally listen and counsel better and that they are more practical and have better reality testing. Since they might have had a harder time getting into residencies, they tend to be brighter and better students on average.

IMPLICATIONS FOR PRACTICE

A Ross Laboratories survey of 2200 third-year pediatric residents in 1988 showed that men and women made similar career choices after residency, with slightly more women choosing salaried positions. However, in the American Academy of Pediatrics survey, subspecialty career choices varied between men and women, with endocrinology (2:1), neonatology (1.5:1), hematology (2:1), and adolescent medicine (2.5:1) being primarily male choices, but developmental and behavioral medicine (1:6) being primarily a female choice. Other subspecialties had a more or less equal distribution of men and women.

The current requirement of 3 years of subspecialty training beyond the 3-year residency program might make it less attractive for women, since many are seeking flexibility in posttraining careers for family purposes. These factors might alter the availability of certain subspecialists and might decrease the pool of excellent candidates. There is also a relative deficiency of female role models in many subspecialties and in higher academic ranks.

Equity in pay, either in practice or in academic medicine at the time of hiring, is extremely important, especially since the gap will increase as raises are based on a percentage of salary. The gap will widen even further if less merit is given to women or if they have a longer time to wait for promotion. Job sharing, which was not viewed as practical during residency, might be one solution for women in practice, since it allows a flexibility that may not be present during residency or in an academic setting. The disadvantage is that it would preclude full partnership in a group practice or promotion and tenure if done in an academic setting. The present male-dominated academic or private practice system must be sufficiently flexible to encourage women who have taken time off to return to full-time work, since there is a finite time for women to bear children and no one else who can substitute. It is no more convenient for a woman in private practice or academic medicine to have children than it is for a woman in her residency. The choice of time of the pregnancy is a part of the woman's personal responsibility to herself and her husband.

The issue of whether a woman joining a group practice or faculty should indicate specific plans for future pregnancy was raised, since some employers consider maternity leave negatively. Mutual honesty coupled with flexibility in the system is the key to successful working relationships.

A national concern that is very pertinent to medicine is that many mothers no longer provide child care the way they once did. This is because other provisions for child care must be sought by working mothers. Most commonly, children of working women are cared for in the homes of other women with young children, by live-in nannies, or in day-

care centers. One study, quoted by Dr Margolis, compared very good day care with a full-time housekeeper and showed no differences in the children's psychological development and maturation even when the children were younger than 3 years. There was actually a significant increase in the ability of these children to be independent. No studies were cited that showed that day care was not as good.

The reality is that women will be out of the house and children will have to be taken care of by others. Therefore, appropriate facilities must be made available. The provision of day care in the hospital setting would be of benefit and might also help recruit nurses to the hospital. High-quality day care is already a recognized stimulus to productivity in general industry.

In the American Academy of Pediatrics survey, a strong negative correlation existed for female pediatricians between the number of children and hours worked. Also, in general, male pediatricians worked 8 to 9 hours per week more than women, who also worked fewer weeks per year. Other studies performed over the past few years supported the finding that women worked fewer hours per week than men, with a range of 1.5 to 7 hours per week less. Concern was raised about the availability of pediatric services for the general population if the trend continues. On the other hand, those concerned that there will be too many physicians saw this work schedule, which is more conducive to a happy family life, as a double advantage. The longer hours of male pediatricians allowed them to see 30 to 40 more patients per week than women, but female physicians earned 14% less than men after correction was made for time worked.

The American Academy of Pediatrics survey not controlled for hours worked or type of practice showed that more than 50% of board-certified and 75% of non-board-certified female pediatricians earned less than \$60 000 per year compared with only 25% of males. It also showed that women were three to four times as likely to interrupt their careers than were men. Seventy percent of women interrupted their careers for child-rearing purposes, and 20% to support a spouse's career.

IMPLICATIONS FOR PERSONAL AND HOME LIFE

Alternatives to full-time employment were discussed. The "mommy track," commonly employed in the business world, is full-time employment or job sharing in which the woman works 8 hours per day but does not work overtime or outside the workplace. This is generally understood to preclude a woman from a full partnership or from achieving tenure in a university. Career sequencing describes a woman professional who establishes herself and then takes 5 to 6 years off to attend to early child rearing. In an ideal setting, she then resumes work in a way that does not conflict with her role as a mother. She essentially preserves her professional identity while foregoing the fast track. Again, the responsivity and flexibility of the system needs to be assured for women who choose this as a career alternative.

Both of these alternatives avoid the issues since they do not address the lack of social support for mothers who work, the role of the father in parenting, and the demand of employers that professional men and women sacrifice part of their personal lives to further their careers. Society still views parenting and domestic work as female roles and expects women to adjust to the conflicting demands of career and home life. The problems women face are viewed as private concerns and not societal issues, whereas in fact these are broad social issues. Issues pertaining to women in pediatrics after residency are identical to those during residency and are common generally to all women in society. Finally, marriage between two professionals involves additional stress for women, since two ideal jobs in the same place are rare, and the woman often compromises her career to accommodate her spouse.

Women professionals have four options for coping with their lives:
(1) They can become the woman who does it all without compromise and risk a great deal of physical and personal stress. (2) They can combine career and family, working less time as a physician and having more time to spend at home.
(3) They may abandon all other concerns for medicine, but this is not pleasurable and/or practical for many women.

(4) They may abandon their profession to become full-time mothers/wives. This last option is hardly practical or desirable for anyone who spends or has spent so much time, effort, and expense achieving professional status.

Many participants thought that the woman who combines career and family with compromise would be happier (as would her husband and children) than the woman who is extremely stressed trying to do it all. However, the compromise should not only be on the part of the woman.

There is also a need for good male role models in medicine. They should communicate how men relate to their wives. participate in child rearing, and share household duties. Many male pediatricians believe that a woman should be home with the children, yet each indi-\ vidual has the right to make decisions about the role of personal life in the context of professional life. To preserve this, maximal career flexibility for men and women must be available when family responsibilities are important. The guilt that many women feel and are made to feel about working outside the home may decrease with each generation or as more experience is gained by those who are successful in combining family and career. It is acceptable for men to combine family and career in our current culture, and there is no reason why the same cannot be true for women as our culture changes.

CONCLUSION

Society needs to actively recognize that the percentage of women in the work force is increasing and make adjustments. Pediatric training program directors need to be creative and provide more flexibility to help female physicians carry out their roles as pediatricians, wives, and mothers. Innovative practice and academic arrangements must be made for women after residency training. Providing a greater quantity of better and more affordable day care needs to be a national priority, and at the same time, more research is needed on the effects of day care, so that children will grow up to be well-adjusted, productive adults. Legislative support must come from pediatric organizations, such as the American Academy of Pediatrics, the American Board of Pediatrics, and the Pediatric Residency Review Committee.

Broad societal problems are occurring because work rules were established in a different era. The task is to change the rules, not help women adjust to them. There are immediate needs for the following: creative scheduling in programs and in the work force, adequate maternity and paternity leave policy, more appropriate female and male role models, seminars on combining careers and parenting for both men and women, emotional support during and after maternity leave, day care in

hospitals, and flexibility for women treturn to careers after full-time or par time leave.

Recognition of the needs of women i pediatrics must lead to programs i meet those needs. These program should serve as models for othe disciplines.

Trends and Implications of Women in Pediatri was the third annual conference on issues in pedia ric education held under the auspices of the Ch dren's Health Center of St Joseph's Hospital as Medical Center, Phoenix, Ariz. It was conduct from October 21 through 23, 1988, in Scottsdal Ariz, and was cosponsored by the Flinn Found tion, Phoenix; Ross Laboratories, Columbus, Ohi Mead Johnson & Co, Evansville, Ind; and Wyet Ayerst Laboratories, Philadelphia, Pa. The ma speakers were Catherine DeAngelis, MD, profe sor and deputy chairman, Department of Pedia rics. The Johns Hopkins University School of Med cine, Baltimore, Md; Vincent Fulginiti, MD, dea Tulane University College of Medicine, New O leans, La, and editor, AJDC; Birt Harvey, Ml president, American Academy of Pediatrics, E Grove Village, Ill; Robert Brownlee, MD, pres dent, American Board of Pediatrics, Chapel Hi NC; Jacqueline A. Noonan, MD, professor as chairman, Department of Pediatrics, University Kentucky School of Medicine, Lexington; and Ma ine Margolis, PhD, professor, Department of A thropology, University of Florida, Gainesville. Tl participants included 35 pediatricians, pediatr department chairmen, and residency progra

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CORRECTION

Incorrect Value.—In the article entitled "Anti-Staphylococcus aureus IgE Anti-bodies for Diagnosis of Hyperimmunoglobulinemia E-Recurrent Infection Syndrome in Infancy," published in the September 1989 issue of AJDC (1989;143:1038-1041), an error appeared in Table 1 on page 1039. In the second to last row in the first column, in the parenthetical statement, the value "<70%" should have been "<10%."

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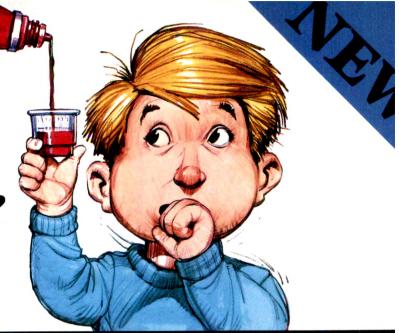
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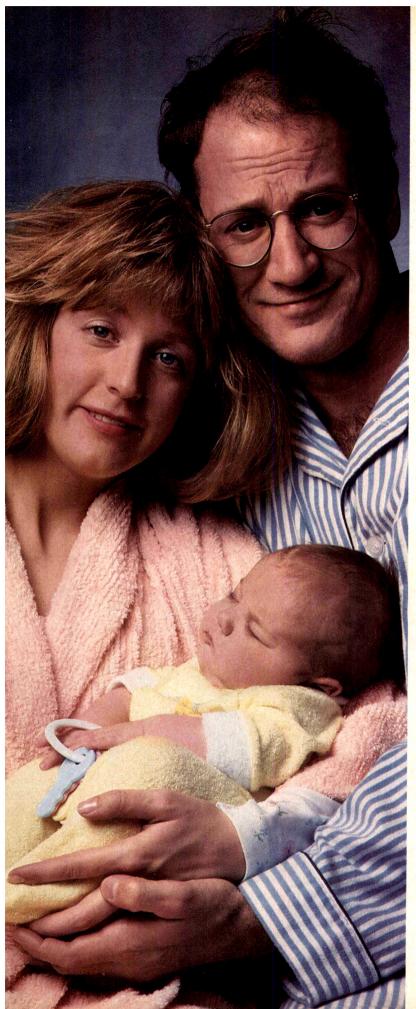
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Pediatric FORMULA 44

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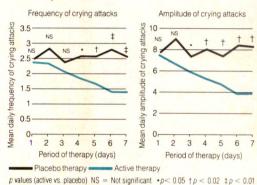
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Kanwaljit SS, Jasbir KS. Simethicone in the management of infant colic.
 Practitioner. 1988;232:508.



Efficacy of Transtelephonic Electrocardiographic Monitoring in Pediatric Patients

Mary Ann Goldstein, MD; Peter Hesslein, MD; Ann Dunnigan, MD

 The results of transtelephonic electrocardiography for transient symptomatic event recording in 61 consecutive pediatric patients (aged 4 months to 21 years) were reviewed. In 13 (21%) of 61 patients, previous arrhythmia diagnoses had been made by electrophysiologic study; monitoring was utilized to evaluate symptoms before or after pharmacological/surgical therapy. Transtelephonic electrocardiography was used to study undocumented symptomatic events consistent with an arrhythmia in the remaining 48 (79%) of 61 patients. Adequate transmissions during symptoms were obtained in 36 (59%) of 61 patients. Goals of monitoring were achieved in all 13 patients with previous diagnoses. Of the 25 of 48 patients without prior diagnoses who provided transmissions during symptoms, 15 had sinus rhythm, while 10 manifested an arrhythmia. Abnormal transmissions were most common in patients with palpitations and never evident in patients with symptoms of chest pain.

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erable diagnostic value in patients with suspected paroxysmal arrhythmias. However, these recordings may be difficult to obtain by conventional continuous ambulatory monitoring if symptoms are infrequent. Indeed, several investigators have reported that 24 to 48 hours of continuous electrocardiographic monitoring seldom permits documentation during symptoms that occur infrequently.¹³

Outpatient transtelephonic electro-

cardiographic monitoring for transient event recording has been recommended for the evaluation of both adult and pediatric patients with infrequent symptoms. ⁴⁸ In this study, we determined the overall efficacy of transtelephonic monitoring for obtaining symptomatic electrocardiographic recordings in a large group of pediatric patients, and we also assessed the diagnostic yield of transtelephonic monitoring according to the type of presenting symptom.

PATIENTS AND METHODS

We reviewed the records of 61 consecutive children and adolescents supplied with transtelephonic monitoring devices from May 1985 to August 1988 at the University of Minnesota, Minneapolis, hospital and clinic. All monitors had been ordered by a pediatric cardiologist for the purpose of monitoring

symptomatic events as detailed below. Two commercial monitoring systems were used during this period (Survival Technology Inc, Bethesda, Md, and CardioCare, Queens, NY). Both systems consisted of a small handheld or clip-on portable recorder/playback unit attached to wrist bracelets or underarm electrodes placed at the time of symptoms, or to continuously worn skin surface electrocardiographic leads.

Figure 1 illustrates one type of transtelephonic unit with underarm electrodes. During symptoms, the patient places one electrode under each arm and then presses the record button on the unit. The monitor records the patient's electrocardiogram (modified lead 1) for 30 seconds. At the patient's convenience, telephone transmission is accomplished by calling the appropriate number, placing the telephone mouthpiece to the grille on the monitor, and pressing the play button. Thus, unlike older "real-time" transmitters, immediate access to a telephone at the time of symptoms is not necessary for the

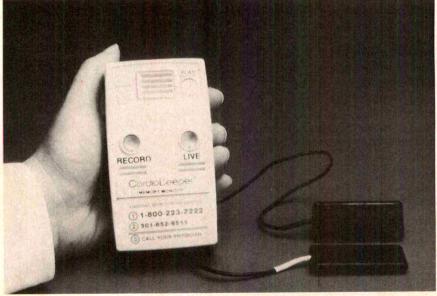


Fig 1.—One type of transtelephonic monitor with underarm electrocardiographic leads. During symptoms, one lead is placed under each arm and the record button is pressed. A 45-second electrocardiographic recording is stored and may be transmitted over the telephone at the patient's convenience.

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success of the monitoring procedure. In this study, patient activation remained a requirement of all devices used; we did not use any third-generation units with automated arrhythmia-sensing and counting algorithms.

Several transtelephonic units capable of continuous surveillance were available and were used. For such continuous memory loop monitoring, patients are connected to the monitor by skin surface electrocardiographic leads at all times. A single electrocardiographic lead is continuously processed into a 70-second memory loop. When the patient activates the event recorder, the electrocardiographic recording beginning 30 seconds before activation is retrieved to a noncycling memory, as is the subsequent 40 seconds of electrocardiogram after activation. In this way, the electrocardiographic recording before symptoms (and the moment of arrhythmia onset, if present) is recorded. These devices are particularly useful in patients whose symptoms are extremely transient or whose symptoms are accompanied by rapid loss of consciousness.

Monitoring periods varied from 2 weeks to 3 months and were determined by the ordering cardiologist. To ensure consistency in interpretation, all transmitted symptomatic recordings were interpreted by one pediatric electrophysiologist.

Clinical Characteristics of the Monitored Patients

Patients ranged in age from 4 months to 21 years (median, 11 years). In the very young patients, transtelephonic transmissions were initiated by a parent who had noted suspicious signs or symptoms. There were 32 male patients and 29 female patients. Of the 61 patients, 15 (24%) had structural congenital heart disease. All patients had prior electrocardiograms demonstrating sinus rhythm. Additionally, ventricular preexcitation (characterized by a short PR interval, a delta wave, and an anomalous QRS morphology) was present on a sinus rhythm electrocardiogram in 7 (11%) of 61 patients.

Previous arrhythmia diagnoses by intracardiac or transesophageal electrophysiologic studies had been made in 13 (21%) of 61 patients. These patients were given transtelephonic monitors to confirm the nature of symptomatic events before or after pharmacological/surgical therapy (12 of 13 patients) or to evaluate antitachycardia pacemaker function (1 of 13 patients).

In 48 (79%) of 61 patients, symptoms consistent with a paroxysmal arrhythmia were present, but there was no previous electrocardiographic documentation during symptoms. The predominant presenting symptom for these subjects was palpitations in 27 subjects, presyncope or syncope in 10 subjects, and chest pain in 11 subjects.

RESULTS

Of all 61 patients receiving transtelephonic monitors, 38 (62%) attempted to record and transmit symptomatic events during their monitoring period. Two (3%) of these patients were unable to obtain an adequate electrocardiogram on any of three attempts. Therefore, transtelephonic monitoring failed to yield diagnostic information in 25 (41%) of 61 patients.

A total of 152 transmissions during symptoms were attempted by 38 patients. Of these, 2 transmissions could not be recorded due to mechanical difficulties, 4 transmissions were uninterpretable due to poor quality, and 6 transmissions (all from one patient who was able to record other symptomatic events with the same standard memory monitor) were unsuccessful because of the transience of the symptoms. Thus, the failure rate for the capture of symptomatic events by individual transtelephonic transmission attempts was 8%.

Pediatric Patients With Previous Arrhythmia Diagnoses by Electrophysiologic Study

In all 13 of these patients, goals of confirming the nature of symptomatic events and antitachycardia pacemaker function were achieved. Transmissions during symptoms were obtained in 11 (85%) of 13 patients. Of note, 6 of 13 patients with a previous arrhythmia diagnosis by electrophysiologic study had sinus rhythm on at least one recording during symptoms. This phenomenon occurred in 3 of 4 infant and toddler patients in this group whose parents were responsible for deciding whether symptoms were present and for performing the transtelephonic transmission.

Figure 2 illustrates a transmission obtained during a syncopal episode by an 18-year-old girl who was wearing a continuously attached memory loop transtelephonic monitoring unit. The patient had a history of recurrent syncope and had inducible polymorphic ven-

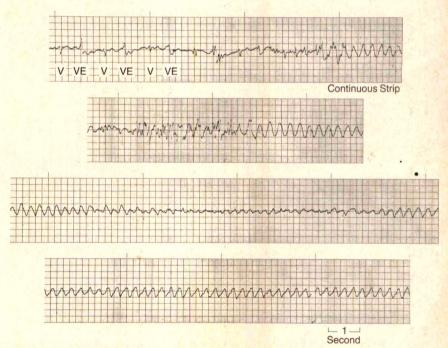


Fig 2.—This record was obtained during syncope in an 18-year-old girl with a history of syncope and inducible polymorphic tachycardia requiring cardioversion on electrophysiologic study. A continuous electrocardiographic strip from a continuous loop monitor is shown. At onset of dizziness, the patient activated the recorder. During the memory portion of the recording, and before syncope, ventricular bigeminy is present. After some artifact, a slightly irregular, wide complex QRS tachycardia with a rate of 210 beats per minute is seen. More artifact is present, and then a polymorphic wide QRS tachycardia that becomes more regular at the end of the recording is evident. The rhythm spontaneously converted to sinus rhythm after the 40-second recording period. After regaining consciousness the patient telephoned in the recording. V indicates R wave of supraventricular beat; VE, ventricular extrasystole.

tricular tachycardia requiring cardioversion on previous intracardiac electrophysiologic study. Because the tachycardia obtained in the catheterization laboratory was difficult to initiate (required ventricular burst pacing) and did not self-terminate in the time allowed, it was unclear whether this rhythm was responsible for the clinical history of recurrent syncope. The polymorphic ventricular tachycardia shown in the transtelephonic recording was similar to the tachycardia seen during electrophysiologic study, except that the clinical arrhythmia spontaneously converted to sinus rhythm some time after the 40-second recording period; the patient regained consciousness and then called in the recording. In this patient, transtelephonic monitoring enabled verification of the arrhythmic basis for syncope and also illustrated the onset of the arrhythmia.

Pediatric Patients Without Documented Arrhythmias

Of these 48 patients, interpretable recordings during symptoms were obtained in 25 (52%). Fifteen of these patients consistently had sinus rhythm during symptoms, while 10 patients had at least one abnormal recording during symptoms. Of these 10 patients with abnormal recordings, 3 exhibited ventricular preexcitation during sinus rhythm. The types of arrhythmias seen in these 10 patients are listed in the following tabulation:

•	No. of
Arrhythmias	Patients
Regular, narrow QRS	
tachycardia	5
Irregular, narrow QRS	
tachycardia	1
Regular, wide QRS	
tachycardia	1
Irregular, wide QRS	
tachycardia	1
Slow junctional rhythm	1
Frequent multiform	
ventricular extra-	
systoles	1

Figures 3 and 4 illustrate transmissions obtained during symptoms in two different patients with histories of palpitations but no previously documented arrhythmias.

The Table summarizes the results of transtelephonic monitoring based on predominant symptom in the 48 pa-

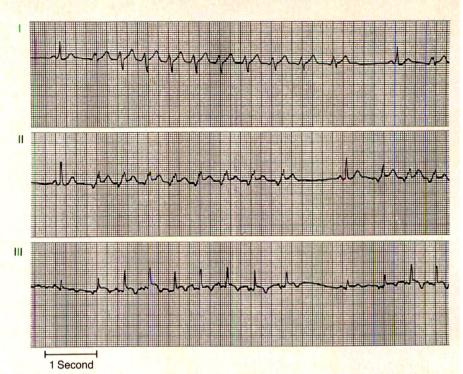


Fig 3.—This symptomatic transmission was obtained in a 17-year-old boy with palpitations. Three nonsimultaneous limb lead electrocardiographic recordings are shown and were obtained by repositioning the electrodes (the "right" electrode under the right arm, "left" electrode at the waist for lead II; the right electrode under the left arm, the left electrode at the waist for lead III). A repeating pattern of one sinus beat followed by an irregular, wide QRS tachycardia (an ectopic atrial rhythm) with a rate of 120 beats per minute is present. Ventricular preexcitation, that is, the presence of a short PR interval, a delta wave, and an anomalous QRS complex is seen on the sinus beats in lead I. Maximally preexcited tachycardia beats are seen in lead II. The P waves preceding the tachycardia beats are not seen in lead I, are negative in lead II, and are biphasic in lead III.

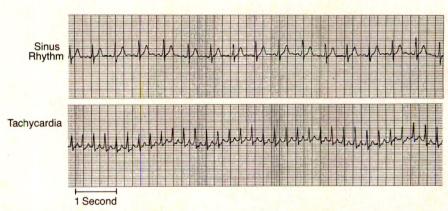


Fig 4.—These recordings were obtained in a 14-year-old boy with a history of palpitations. The patient's baseline recording illustrates normal sinus rhythm with normal QRS morphologic features (top panel). During symptoms, a regular, narrow complex QRS tachycardia with a rate of 214 beats per minute was obtained (bottom panel).

tients without previous arrhythmia documentation. Almost all abnormal transmissions were obtained in pediatric patients with histories of palpitations. Only one patient with presyncope or syncope had an abnormal transmission during symptoms, and most patients with presyncope/syncope had no trans-

Outcome of TTM by Sumptom in Patients With Clinically Suspected but Undocumented Arrhythmias*

		Symptoms	
Outcome	Palpitations (n = 27)	Presyncope/Syncope (n = 10)	Chest Pain (n=11)
Arrhythmia on TTM (n = 10)	9	1	0
Sinus rhythm on TTM (n = 15)	6	3	6
Inadequate TTM (n=2)	1	0	1
No symptomatic TTM (n = 21)	11	6	4 .
No. (%) of patients transmitting interpretable records during symptoms	15 (55)	4 (40)	6 (55)

^{*}TTM indicates transfelephonic monitoring.

missions during their monitoring period (6 of 10 patients). In contrast, no patient with a history of chest pain had an abnormal transmission; all 6 patients who sent an adequate record had sinus rhythm during symptoms. The predominant symptom had no discernible bearing on the proportion of patients able to record and transmit symptomatic events

Average duration of transtelephonic monitoring in the same 48 patients was compared based on the predominant presenting symptom. In patients obtaining transmissions during symptoms, average duration of monitoring was 1.47 months in patients with palpitations, 1.50 months in patients with presyncope/syncope, and 1.14 months in patients with chest pain. Average duration of monitoring in patients who did not transmit was similar: 1.27 months in patients with palpitations, 1.67 months in patients with presyncope/syncope, and 1.00 month in patients with chest pain.

χ² Analysis of the percentage of patients having an abnormal transmission (clinically significant arrhythmia as listed in the tabulation) during the appearance of symptoms based on predominant symptom was performed using Fisher's Exact Test. There was no statistical difference between the percentage of patients with an abnormal transmission and a history of palpitations (9 of 15) and patients with a history of presyncope/syncope (1 of 4) (P = .3). Similarly, the percentage of patients having an abnormal transmission and a history of presyncope/syncope (1 of 4) and those with a history of chest pain (0 of 6) were not statistically different

(P=.4). However, statistical differences in percentages of patients with an abnormal transmission during symptoms and histories of palpitations (9 of 15) and chest pain (0 of 6) were observed (P=.018).

The number of symptomatic transmissions per patient varied depending on the predominant symptom. Of patients who obtained transmissions during symptoms, those with palpitations and presyncope or syncope had an average of 2.20 and 2.25 transmissions per patient, respectively. Patients with chest pain (excluding one patient with 39 transmissions) had, on average, 3.67 transmissions per patient. Thus, patients with chest pain transmitted almost twice as many recordings as other patients, despite being monitored for a slightly shorter period.

COMMENT

Our data showed that 85% of pediatric patients with previously documented arrhythmias and 52% of the pediatric patients with suspected but undocumented arrhythmias (62% overall) obtained transtelephonic recordings during symptoms using the newer "memory" type units. Similarly, earlier studies utilizing "real-time" monitors have reported that 48% of adults and 51% of pediatric patients with clinically suspected but undocumented arrhythmias obtained transmissions during symptoms. 7,8 Other reports on pediatric transtelephonic monitoring have discussed the interpretation of transtelephonic recordings from small numbers of patients4,6 rather than the capability for such monitoring to obtain electrocardiographic documentation during

symptoms in a large group of patients with varying symptoms. Our evaluation of transtelephonic monitoring by type of predominant symptom provides an additional perspective on the usefulness of transtelephonic monitoring in selected patients as well as on the nature of the clinical problem being investigated.

In our study, 55% of pediatric patients with palpitations (15 of 27) and chest pain (6 of 11) transmitted interpretable electrocardiograms during symptoms. However, transmissions in patients with palpitations were highly associated with arrhythmias while all transmissions from patients with chest pain demonstrated sinus rhythm. Arrhythmias from patients with palpitations were revealed despite the fact that these subjects transmitted on average half as many records per individual as did patients with chest pain.

The greater yield of arrhythmias during transmissions from patients with a history of palpitations may have been related, in part, to the fact that 4 of these 27 patients exhibited ventricular preexcitation during sinus rhythm. The presence of a known substrate for tachycardia in patients with a history of palpitations would naturally be expected to yield a certain proportion of abnormal symptomatic transmissions. Indeed, 3 of the 4 patients with ventricular preexcitation in this group had symptomatic transmissions illustrating an arrhythmia. Since this study did not address the length of time necessary to obtain a symptomatic transtelephonic transmission or control for length of monitoring periods between groups of patients, it is possible that differences in duration of monitoring affected our results. On the other hand, our study may accurately reflect a true relative absence of cardiac pathologic features as the basis of chest pain in pediatric patients, as has been recently reported in a large prospective study.

Nevertheless, the lack of abnormal symptomatic transmissions in patients complaining of chest pain does not diminish the usefulness of transtelephonic monitoring in these patients. We have found that transtelephonic monitoring often provides reassurance of the absence of an arrhythmia during symptoms in an easy and noninvasive manner. Additionally, at our institution,

costs of transtelephonic monitoring (\$295 for 1 month of enrollment, unlimited emergency transmissions) compare favorably to that of 24-hour continuous outpatient electrocardiographic monitoring (\$430).

Evaluation of the efficacy of transtelephonic monitoring in our patients with histories of presyncope or syncope is problematic in that 6 of 10 of these patients were asymptomatic during their monitoring period. While any normal or abnormal symptomatic rhythm recording is diagnostically useful, the relative infrequency of symptomatic transmissions (and possibly symptoms) may not permit adequate diagnosis by this method alone. Because of the life-threatening potential for some forms of syncope, other diagnostic investigations, including intracardiac electrophysiologic study with evaluation of the patient's response to upright tilt, may be warranted.10

Finally, transtelephonic monitoring appeared to be particularly useful in our patients with previous arrhythmia diagnoses. It was apparent that in more than half of these patients, and in mostly infant or toddler patients, symptomatic transmissions illustrated sinus tachycardia as opposed to the previous arrhythmia diagnosis on at least one occasion. This information was extremely

helpful in our assessment of medical or surgical management and in pointing out the difficulties of determining true incidence of arrhythmia even after an arrhythmia diagnosis has been made.

CONCLUSION

Our data suggest that transtelephonic electrocardiologic monitoring is
effective in obtaining symptomatic
transmissions in many pediatric patients under investigation for suspected
arrhythmias and is helpful in managing
patients with previous arrhythmia diagnoses. Transtelephonic monitoring may
be valuable to demonstrate the absence
of an arrhythmic basis for a patient's
symptoms as well as to document the
arrhythmia responsible for those symptoms.

We did not specifically address the issue of length of time necessary to obtain a symptomatic transtelephonic transmission. Our impression is that duration of monitoring should be determined by the severity and frequency of each patient's symptoms as well as the clinician's opinion as to how likely it is that the symptoms are related to a paroxysmal arrhythmia. Clearly, individual clinical assessment must play an important role in how transtelephonic monitoring is utilized.

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A Comparison of Chromogen Test Strip (Chemstrip bG) and Serum Glucose Values in Newborns

Paul C. Holtrop, MD; Kimberly A. Madison, RNC; Frederick L. Kiechle, MD, PhD; Raymond E. Karcher, PhD; Daniel G. Batton, MD

 Although glucose oxidase-peroxidase chromogen test strips are frequently used to estimate serum alucose values in newborns, previous studies have not evaluated multiobserver variability of test strip readings and have included few infants with hypoglycemia. We compared values of 272 samples of serum glucose with values simultaneously obtained by chromogen test strips (Chemstrip bG) in newborns. The diagnostic sensitivity of a chromogen test strip less than 2.2 mmol/L for predicting a serum glucose level less than 1.9 mmol/L was 86% (95% confidence interval [CI], 75% to 94%), with 78% specificity (95% CI, 73% to 84%). The positive predictive value in our specimens, with a 21% prevalence of serum glucose levels less than 1.9 mmol/L, was 52% (95% Cl, 41% to 62%), with a negative predictive value of 95% (95% CI, 91% to 100%). Fiftyeight of our serum glucose values were less than 1.9 mmol/L and the levels obtained by chromogen test strip were greater than or equal to 2.2 mmol/L in 8 of these cases. Review of these 8 cases showed that a delay in performing the laboratory glucose oxidase serum glucose could account for the discrepancy in 2 cases. Chromogen test strips are readily available and easy to use, but more sensitive, specific, accurate, and precise methods of serum glucose screening in newborns are needed.

(AJDC. 1990;144:183-185)

R apid estimation of blood glucose in neonates by using glucose oxidase-peroxidase chromogen test strips (Chemstrip bG, Boehringer Mannheim, Indianapolis, Ind) is a common practice in most nurseries and neonatal intensive care units. The value of this method for monitoring blood glucose in diabetic patients is well established, but questions remain about its validity in newborns. Data documenting the sensitivity of these tests for identifying

Acc∈pted for publication September 11, 1989. From the Division of Newborn Medicine, Department of Pediatrics (Drs Holtrop and Batton and Ms Madison), and the Department of Clinical Pathology (Drs Kiechle and Karcher), William Beaumont Hospital, Royal Oak, Mich.

Reprint requests to the Division of Newborn Medicine, Department of Pediatrics, William Beaumont Eospital, 3601 W 13 Mile Rd, Royal Oak, MI 48072 (Dr Holtrop). hypoglycemia are lacking, and the reliability of this method when used by multiple observers, rather than a few research personnel, has not been well evaluated. The purpose of this study was to compare the chromogen test strip method of determining blood glucose levels in neonates, as performed by bedside nurses, with the central laboratory method.

METHODS

We collected data from April 1988 to August 1988 in the newborn observation, intermediate, and intensive care nurseries. When clinically indicated, blood samples were drawn for serum glucose determination and tested simultaneously by chromogen test strips. Most blood specimens were obtained via heelstick, some by venipuncture, and some from an umbilical artery catheter (if no dextrose was infusing through the catheter).

The nurse caring for the infant performed the chromogen test strip determinations according to the manufacturer's instructions. A drop of blood covering both test pads was applied to the chromogen test strip. After 60 seconds, the nurse wiped the blood from the test strip with a cotton gauze and, 60 seconds later, matched the chromogen test strip to the color scale on the vial. Results may be read as corresponding to an exact reading, eg, 4.4 mmol/L, or as being within a range of values, eg, greater than 2.2 mmol/L to less than 4.4 mmol/L. The ranges are narrow in the low end of the scale, and widen progressively as the glucose value increases (Table 1). Approximately 50 nurses were involved in the study.

Blood samples for serum glucose determinations were collected in 1-mL plain plastic tubes with serum separating-gel at the base (Microtainer, Becton Dickinson & Co, Rutherford, NJ) and delivered to the laboratory at room temperature. The mean time, from sample collection to completion of serum glucose analysis, was 51 minutes (SD, ± 25 minutes). Serum glucose values were determined in the laboratory by the Beckman glucose analyzer (Beckman Instruments Inc, Brea, Calif) (glucose oxidase method). Hematocrits were recorded if they had been performed within 12 hours of the glucose determination.

We tested multiobserver variability of reading chromogen test strips by obtaining nine blood specimens, with serum glucose values ranging from 0.7 mmol/L to 23.9 mmol/L, from the laboratory. A chromogen test strip evaluation was performed on each specimen by one of the investigators and then independently shown to 10 nurses. Seventy-six of the 89 readings were in agreement, while the remaining 13 readings differed by no more than one range of values.

DATA ANALYSIS

Data analysis was divided into two areas: (1) examining agreement between methods, and (2) examining the value of chromogen test strips as a screen for hypoglycemia. We used a scattergram to give a visual display of the data. However, since linear regression does not predict agreement between two methods.2,8 we also used a checkerboard grid to display agreement between chromogen test strip and serum glucose values.4 For the checkerboard display, any discrete value obtained by a chromogen test strip reading was included in the next highest range (eg, 2.2 mmol/L is included in the greater than 2.2- to less than 4.4mmol/L range). To determine the value of chromogen test strips for predicting hypoglycemia, we examined the sensitivity (true positives/[true positives+ false negatives]), specificity (true negatives/[true negatives + false positives]), positive predictive value (true positives/[true positives+false positives]), and negative predictive value (true negatives/[true negatives+false negatives]) of the measurement.5 For this purpose we used a serum glucose value of less than 1.9 mmol/L as the definition of hypoglycemia.6 A true-positive test result was defined as a chromogen test strip value less than 2.2 mmol/L (the chromogen test strip value closest to the defined value for hypoglycemia) and a serum glucose value less than 1.9 mmol/L. A false-positive result was defined as a chromogen test strip value less than 2.2 mmol/L and a serum glucose value greater than or equal to 1.9 mmol/L. A true-negative result was defined as a chromogen test strip value greater than or equal to 2.2 mmol/L and

a serum glucose value greater than or equal to 1.9 mmol/L. A false-negative result was defined as a chromogen test strip value greater than or equal to 2.2 mmol/L and a serum glucose value less than 1.9 mmol/L.

When a chromogen test strip reading was a range, eg, greater than 1.1 to less than 2.2 mmol/L, the mean of that range was used for data analysis (eg, 1.7 mmol/L for a value recorded as >1.1 to <2.2 mmol/L). A two-tailed t test was used to compare differences in collection times between groups.

RESULTS Agreement Between Methods

A total of 272 sets of simultaneous serum glucose and chromogen test strip values were obtained from 126 newborns. The Figure displays the scattergram of the data. Table 2 is a checkerboard analysis displaying the number of chromogen test strip values in a given range vs the number of serum glucose

Table 1.-Ranges for Recording Chromogen Test Strip (Chemstrip bG) Results mmol/L >0 to <1.1 11 >1.1 to <2.2 2.2 >2.2 to <4.4 4.4 >4.4 to <6.7 6.7 >6.7 to <10.0 10.0 >10.0 to <13.3 13.3

>13.3 to <22.2

22.2

>22.2

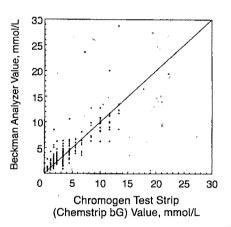
values within that range. The chromogen test strip value and the serum glucose value were within the same range 61% of the time.

Multiple regression analysis showed no effect of hematocrit on correlation of chromogen test strip values with serum glucose values.

Screening for Hypoglycemia

There was a 21% prevalence of hypoglycemia, ie, serum glucose level less than 1.9 mmol/L. The sensitivity of chromogen test strips for detecting hypoglycemia was 86% (95% CI, 75% to 94%) with a specificity of 78% (95% CI, 73% to 84%). The positive predictive value of the chromogen test strip for predicting hypoglycemia was 52% (95% CI, 41% to 62%), with a negative predictive value of 95% (95% CI, 91% to 100%).

There were eight instances of falsenegative samples, ie, chromogen test strip values greater than or equal to 2.2 mmol/L and serum glucose values less



Scattergram with line of equality, plotting Beckman glucose analyzer values vs chromogen test strip (Chemstrip bG) values.

than 1.9 mmol/L (Table 3). There was no significant difference in the mean time between collection and analysis of the false-negative samples vs that of the entire group (55 minutes vs 52 minutes, P=.58), nor in the mean time between collection and analysis of the false-negative samples vs true-positive samples (55 minutes vs 49 minutes, P=.42).

Uncentrifuged blood, allowed to stand at room temperature and permitted to clot, may have a mean decrease in serum glucose of 7% in 1 hour. In two of the false-negative samples (samples 1 and 3), the amount of time elapsed between collection and analysis of the specimen may have accounted for the discrepancy between the chromogen test strip and serum glucose value. Reclassifying these two tests as true negatives instead of false negatives changes the sensitivity to 90% from 86%, and has no effect on specificity.

COMMENT

Hypoglycemia, both symptomatic and asymptomatic, has potentially damaging effects in the newborn8; thus, frequent screening of infants at risk is recommended. Most nurseries use a rapid test strip method for this purpose, since it is not practical to perform multiple laboratory serum glucose determinations on the large number of infants who require screening. Herrera and Hsiang evaluated three test-strip methods for blood glucose screening in newborns. They had no false negatives with visual inspection of the Chemstrip bG chromogen test strip, and concluded that this was the best screening method of those studied. However, they had only 18 hypoglycemic samples, and the chromogen test strip determinations were

Table 2.—'Checker	board' Analys	sis of Results (n = 272) Obtained With Chromogen Test Strip (Chemstrip bG) and
		the Beckman Glucose Analyzer
		Beckman Glucose Oxidase Analyzer, mmol/L

Observation			Bed	ckman Glucose C	xidase Analyzer	, mmol/L		
Chemstrip bG, mmoi/L	0-1.08	1.09-2.19	2.20-4.41	4.42-6.63	6.64-9.96	9.97-13.29	13.30-22.17	≥22.18
0-1.08	10	4	2			-		
1.09-2.19	5	50	27	2	1			
2.20-4.41	2	12	72	. 8	•			
4.42-6.63		1	16	14	3	1		
6.64-9.96			3	4	, 7	1		
9.97-13.29				2	8	10	1	
13.30-22.17					1	1	2	1
≥22.18	•						1	

Table 3.—Chromogen Test Strip (Chemstrip bG) Values, Serum Glucose Values, and Analysis Times for False-negative Chemstrip bG Samples

Sample No.	Chemstrip, mmol/L	Serum Glucose, mmol/L	Analysis Time, min
1	2.2	1.9	56
2	2.2	1.7	7
3	2.2	1.7	87
4	>2.2-<4.4	1.8	36
5	>2.2-<4.4	0.9	94
6	>2.2-<4.4	0.8	22
7	>2.2-<4.4	1.8	40
8	>2.2-<4.4	1.4	42

performed by only three observers. Perelman et al, 10 using multiple observers, also compared different test strips, and found no false negatives with Chemstrip 5G chromogen test strips among 6 hypoglycemic samples. As we used multiple observers and had a large number of hypoglycemic samples, we believe our experience more closely reflects the usual practice in nurseries and therefore is a more realistic estimate of its sensitivity and specificity.

Sensitivity is an index of a diagnostic test's ability to detect disease when it is present. Thus, sensitivity of 90% means that 90% of the hypoglycemic babies in our series were detected by chromogen test strip screening, and that 10% of them were missed.

The negative predictive value of a test refers to how well a negative test result correctly predicts the absence of disease. Our negative predictive value of 95% means that 95% of the time that a chromogen test strip value was negative for hypoglycemia (ie, ≥2.2 mmol/L), the serum glucose value was also negative (ie, ≥ 1.9 mmol/L). Similarly, the positive predictive value refers to how well a positive test result correctly predicts the presence of disease. Our positive predictive value of 52% means that 52% of the time that a chromogen test strip value was positive for hypoglycemia (ie, <2.2 mmol/L), the serum glucose value was also positive (ie, $<1.9 \,\mathrm{mmol/L}$).

Positive and negative predictive values will vary according to the prevalence of disease in the population, but sensitivity and specificity remain constant. The prevalence of hypoglycemia in our study population was 21%. If the prevalence of hypoglycemia were less than 21%, as would be expected in a

normal newborn population, the positive predictive value would decrease and the negative predictive value would increase.

It is disconcerting that in our study eight serum glucose values less than 1.9 mmol/L were not predicted by a chromogen test strip value less than 2.2 mmol/L. In these cases either the chromogen test strip value could have been falsely high or the serum glucose value falsely low. There are several errors that can be made in chromogen test strip determinations, including improper timing, inadequate covering of the test strip with blood, using outdated chromogen test strips, comparing a chromogen test strip with a color code from a different batch of chromogen test strip, and examiner color blindness. Although proper orientation of the nursing staff may keep these errors to a minimum, it seems inevitable that, with a large number of observers and samples, collection and reading errors will sometimes occur. A delay in performing the glucose oxidase determination may lower the glucose value through glycolysis. We believe this may account for the false-negative chromogen test strip readings in two of the eight specimens, but probably not in the other six samples.

One could increase the sensitivity of chromogen test strips for detecting hypoglycemia by defining a positive chromogen test strip value as less than or equal to 2.2 mmol/L. However, doing so only increased the sensitivity from 90% to 91%, and the negative predictive value from 95% to 97%, while decreasing the specificity to 61% and the positive predictive value to 39%.

Confirmatory laboratory glucose values should be obtained liberally with low or borderline chromogen test strip values. What constitutes a low or borderline value may change according to the presence or absence of signs of hypoglycemia in the infant, and the definition of hypoglycemia used, which will vary according to the age of the child and the study cited. 6,8,11-13 Recently, other methods for rapidly evaluating "Glucose values" in newborns, the Accuchek II Glucose Reflectance Meter¹⁴ (Boehringer Mannheim Diagnostics, Indianapolis, Ind) and Yellow Springs Instrument Glucose Analyzer¹⁵ (Yellow Springs [Ohio] Instrument Co Inc), have shown promising results. Chromogen test strips, because of their ease of use and wide availability, currently have a role in screening for glucose homeostasis in newborns, but more accurate and precise methods are needed.

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Blood Lead, Calcium Status, and Behavior in Preschool Children

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• To determine if calcium status is associated with blood lead levels and behavlor, 64 black urban children aged 18 to 47 months were studied. Twenty-seven controis (blood lead levels, <1.45 umol/L) were compared with 37 cases (blood lead levels, ≥1.45 µmol/L) with respect to four calcium measures (calcium intake, serum calcium level, 1,25-dihydroxyvitamin D level, and bone densitometric findings) and three behavioral scores. Levels of 25hydroxyvitamin D provided a measure of vitamin D sufficiency. As expected, blood lead level was associated with pica scores. However, none of the calcium measures differed between cases and controls. Controlling for four confounders (season, pica score, maternal education, and sex), yielded no significant differences between the two groups in the mean values of 25-hvdroxvvitamin D and 1,25dlhydroxyvitamin D level. There was no Interaction between blood lead level and the four covariates. No relationship could be demonstrated between calcium status and the pica scores.

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Pica has been demonstrated to increase an individual's lead burden in an environment with lead contamination. ¹⁹ Calcium status is also believed to affect lead levels, but this has been less well documented. Decreased calcium intake has been demonstrated to correlate with increased lead absorption, presumably because of competition of calcium and lead for shared absorptive intestinal receptors. ¹⁰⁻¹² Moreover, the two factors may be related. Animal

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Reprint requests to Columbia University, Harlem Hospital Medical Center, 506 Lenox Ave, New York, NY 10087 (Dr Laraque). studies have revealed a direct relationship between decreased calcium intake and lead pica. An inverse relationship between blood lead level and vitamin D intake, serum calcium level, 25-hydroxyvitamin D (25[OH]D) level, and 1,25-dihydroxyvitamin D (1,25[OH]D) levels has also been noted. In Direct impairment of 1,25(OH)D biosynthesis in the kidneys by lead has been implicated as a mechanism for the inverse relationship between blood lead level and 1,25(OH)D level. Reduced serum 1,25(OH)D level would then result in a negative calcium balance.

While animal studies suggest an important interrelationship between pica, calcium status, and blood lead level, the few studies performed in children have not yielded consistent results. ^{10,11,14} This study tested the specific hypothesis that blood lead level is inversely correlated with calcium status. A secondary aim was to test whether calcium intake is inversely associated with pica.

SUBJECTS AND METHODS

Two groups of children were selected on the basis of their lead levels (controls, <1.45 µmol/L; cases, ≥1.45 µmol/L) and compared. Children between the ages of 18 and 48 months were recruited from two sites: the general pediatric and lead poisoning clinics at the Children's Hospital of Philadelphia (Pa). Eligibility was determined from a chart review, cuestionnaire, and physical examination. Because of known differences in skeletal mass and serum vitamin D values between blacks and nonblacks, only black children were recruited. 15,16 Exclusion criteria were set to eliminate children with other reasons for changes in the factors of interest, that is, children with metabolic bone disease, renal disease, those taking anticonvulsant, diuretic, or steroid therapy, those who had severe psychomotor impairment (limiting the ability to exhibit pica), and those who had received chelation therapy in the month preceding the study.

Data Collection

At enrollment, parents were asked to give informed consent for participation in a four-

part data collection that included a parent questionnaire, blood drawing, dietary history, and bone densitometry. This data collection was designed to provide information in the following areas. Sociodemographic information included age and sex of the child, composition of the household, the mother's educational level, the season at the time of the study, the child's sex, medical insurance coverage, and income. 17,18 The specific questions used in the development of a pica score were derived from the Richman-Graham Behavior Screening Questionnaire and Parent Checklist, with some modifications. 19-21 These questions have been shown to have acceptable validity and reliability in a population-based study. 19 A pica score, reflecting ingestion of nonfood substances, a mouthing habits score, and a general behavior score that included all other items were used to estimate various behaviors. The pica questions involved eating nonfood substances (scored as 0, 1, or 2 [never, sometimes, or frequently]) and eating specific items (paper, toys, dirt, and paint chips) (scored as no [0] or yes [2] for each item). The questions on mouthing habits included sucking objects, drinking from a bottle or cup, sucking thumb or fingers, and biting nails (all scored as 0, 1, or 2 [never, sometimes, or frequently]). The pica, habits, and general behavior scores were an 11-point (range, 0 to 10), a 3-point (range, 0 to 2), and a 23-point (range, 0 to 22) scale, respectively. In the case of the pica score, for example, 0 indicated none and 10 indicated a high degree of pica behavior.

Whole blood was sent to the laboratory of the Department of Health of the City of Philadelphia for measurement of lead by atomic absorption spectrophotometry. 22-24 Calcium status included four measures: calcium intake, serum calcium level, 1,25(OH)₂D level, which is known to regulate calcium absorption, and bone mineral density, as a measure of total-body calcium level. 25-27 A measure of vitamin D sufficiency was obtained with 25(OH)D. A trained nutritionist, without knowledge of the patients' blood lead levels, cbtained anthropometric measurements28,28 and a 24-hour dietary recall. She instructed parents in the use of a 4-day dietary record that included 2 weekend days and 2 weekdays. 30-34 At least two telephone calls were made to the parent to ensure accurate completion and return of the dietary record. The Massachusetts Nutrient Data Bank analyzed the dietary data. 35 Blood was drawn 3 hours

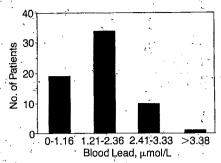


Fig 1.—Blood lead distribution in the study.

postprandially, and serum samples for vitamin D were stored at -20°C and subsequently analyzed in two batches. The serum concentration of 25(OH)D was measured by competitive protein binding assay using rat serum. 26,37 The concentration of 1,25(OH),D was measured by competitive protein binding microassay using calf thymus.38 A bone mineral analyzer (Lunar Radiation model SP-2) using the technique of single-photon absorptiometry was used to measure bone mineral density of the radius in the nondominant forearm. 25,26,89,40 The radius was scanned at the standard midradial site, defined as one-third the length of the forearm proximal to the wrist.

Statistical Analysis

Data were analyzed by means of the Statistical Package for the Social Sciences and BMDP statistical software. 41,42 The χ^2 test for categorical measures (lead group, sex, season, and medical coverage) and t test for interval measures (age) were used to determine comparability of study participants and nonparticipants. The relationship between lead status and calcium measures was tested with the t test for interval level data (number of children/adults in household, calcium intake, vitamin D intake, 25[OH]D level, and 1,25[OH]₂D level) and the Mann-Whitney Utest for ordinal data (maternal education, pica, habits, and general questions scores). 3 The relationship between calcium intake and pica score was examined with Spearman's correlation coefficients and tested for significance. Cases and controls were also tested for differences in 25(OH)D and 1,25(OH),D levels after controlling for sex, maternal education, season, and pica score as covariates in an analysis of covariance. A power analysis showed that our sample size would be able to detect as small as 0.75 SD between the two lead groups at $\alpha = .05$ and $\beta = .20$. Such a difference would be equivalent to approximately 31.21, pmol/L of 1,25(OH), D, 6.64 mmol/L and 4.82 mmol/L of calcium as recorded in a 24-hour dietary recall and 4-day dietary record, respectively, and 0.077 mmol/L of serum calcium. Differences less than these are not believed to be clinically significant.

	Mean	٠.	
	Controls* (n = 27)	Cases* (n=37)	P
Age, mo	28.6 ± 8.5	30.5±9.6	.42
No. of adults/household	2.4±1.2	2.2±1.3	.56
No. of children/household	2.6 ± 1.6	3.3 ± 1.7	.09
Maternal education, y	12:1 ± 1.4	, 11.5±1.1	.07
Behavior scores Pica	2.4±2.8	4.2±3.4	.01
Paint chips	0.15±0.5	$0.89 \pm 1.0^{\circ}$.0009
Mouthing habits	1.0±0.6	1.2±0.6	.19
General questions	8.9 ± 2.3	9.6±3.3	47
Mean serum calcium, mmol/L	2.54 ± 0.11 (27)	2.52 ± 0.09 (27)	.55
Mean calcium intake, mmol/d 24-h recall	17.0±8.2 (27)	17.4±9.5 (35)	.88
4-d record	14.3±6.3 (21)	14.8 ± 6.5 (27)	.82
Mean vitamin D intake, IU 24-h recall	282.6±215 (27)	252.0±189 (35)	.56

*Controls had blood lead levels less than 1.45 µmol/L; cases, 1.45 µmol/L or greater. Numbers in parentheses are numbers of subjects.

331:6 ± 183 (21)

RESULTS

4-d record

The sample consisted of 64 black, urban, and predominantly low-income children. Of the 100 eligible patients approached, 13 refused participation and 23 were excluded (2 had renal disease, 5 were taking anticonvulsants, 4 had severe psychomotor retardation, 6 had metabolic diseases, 5 did not have appropriate guardians available to give informed consent, and 1 had received chelation therapy less than 1 month before the study enrollment time). Of the 64 patients in the study, 4 failed to undergo bone densitometry due to logistic constraints. In addition, while 62 participants completed the 24-hour dietary questionnaire, 48 (75%) completed the 4-day dietary record. Those who refused participation in the study did not differ from the study population with respect to age, sex, lead group, season, or medical coverage. Those with incomplete data did not differ from those with complete data.

The 64 children (36 boys and 28 girls) had a mean age of 29.7 months, with a range of 18 to 47 months. Blood lead levels ranged from 0.58 to 3.86 µmol/L, with a mean value of 1.69 µmol/L. The blood lead level distribution was skewed as illustrated in Fig 1. Lead cases and controls differed on two behavior measures (Table) but did not dif-

fer demographically with respect to medical coverage, income, number of children per household, maternal education, or number of adults in the household. Eighty-three percent of the families received Medicaid, and 74% had incomes less than \$10 000. Three behavior scores and a subscore of the pica score (the paint chips score) were compared for the two groups with low and high lead levels. Both the pica and the paint chip scores were significantly higher in cases. Although the scores on habits and other questions were higher in cases, these differences did not reach statistical significance.

248.5 ± 201 (27)

The dietary analysis revealed a population with recommended daily intake of energy, phosphate, magnesium, and iron, but with excessive intake of total fat, sodium, and protein. Of relevance to this study was evidence of a decreased intake of calcium and vitamin D in both study groups (as compared with the recommended daily allowance for calcium and vitamin D of 20.0 mmol and 400 IU, respectively), with no significant differences detected between the groups. In addition, no differences were found between the groups with low and high lead levels with regard to serum calcium level, 25(OH)D level, or 1,25(OH)D level (Table, Fig 2). Varying the cutoff point between the low and high blood lead level groups (eg. to 2.41 µmol/L) had no

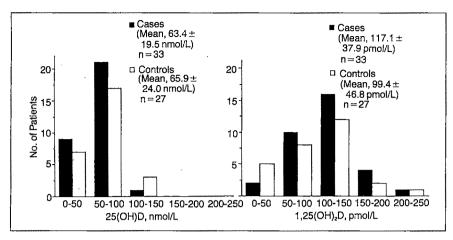


Fig 2.—Serum 25-hydroxyvitamin D (25[OH]D) and 1,25-dihydroxyvitamin D (1,25[OH]₂D) levels of cases and controls. Differences in mean values between cases and controls were tested for significance by means of Student's t test; P=.62 for 25(OH)D and P=.11 for 1,25(OH)₂D.

effect on the results. When bone mineral density is plotted against age for the two groups of children with low and high blood lead levels, the linear regressions of the data do not differ significantly (F = 0.465, P = .631). As expected, vitamin D intake and serum 25(OH)D values were positively and significantly correlated (r=.39, P=.002). Because of the possible seasonal variation of serum vitamin D level, 43,44 season was used as a dichotomous confounder along with four other covariates (sex, maternal education, pica score, and vitamin supplementation) in an analysis of covariance to control for the effects of these váriables on the relationship between lead level and 25(OH)D and 1,25(OH)2D levels. The analysis revealed that there was no significant difference between the lead groups with respect to four of the covariates and no interaction between lead and these covariates. However, in the case of vitamin supplementation, a differential effect was found for the cases and the controls. Mean 25(OH)D levels for the cases and controls were comparable for those not receiving vitamin supplementation. However, vitamin supplementation for the cases raised the mean 25(OH)D levels by 7.86 mmol/L as compared with 24.31 mmol/L for the controls. No association was found between calcium intake and the pica score.

COMMENT

The relationship between pica and lead poisoning in children has been recognized for many years. 1,8,9 This study

again verifies the positive association between blood lead levels and the pica scores. In fact, these scores were the only factors associated with blood lead levels. In our population of children with decreased calcium intake, we were unable to document a relationship between blood lead levels and calcium intake. Previous studies have vielded conflicting results. Sorrell et al,10 in an initial study in which blood lead levels ranged from 0.82 to 7.72 µmol/L, detected a significant difference in calcium intake values only between class III/IV and class I. Comparison of the blood lead distribution of that study to ours yielded a χ^2 value of 9.77, significant at $\alpha = .05$. In a later study by Rosen et al¹¹ in which the blood lead level range was 0.48 to 5.79 µmol/L with a distribution similar to that in our study ($\chi^2 = 1.66$), no difference in calcium intake or 25(OH)D level was found between any of the classes of lead. However, 1,25(OH).D values were found to differ significantly between both classes II and I and classes III/IV and I. We cannot comment on Rosen and associates' findings for the highest lead level group, as we only had five patients who fit this definition, but our results did differ from theirs if we consider only the range for which our studies are comparable. In another study, Mahaffey et al45 reported a weak negative correlation between blood lead levels and calcium intake, but the variance of blood lead level was better explained by height, race, examination date, and sex of the child.

The relative lack of class III/IV pa-

tients in our study does not alone explain the absence of a finding of an inverse relationship between blood lead levels and 1,25(OH). D level. One possible explanation is that the calf thymus assay for 1,25(OH),D used in this study is more sensitive to the dietary form of vitamin D than is the chick assay technique used in other studies.40 In our sample, 52% of the children were taking vitamin D supplementation. At the time of this study, an informal survey of vitamin D supplementation (done by M.N. and A.T.) showed that approximately half of the vitamin D supplementation was in the form of ergocalciferol; therefore, the chick assay could underestimate the level of 1,25(OH), D, especially for children receiving such supplementation. A difference in assays may be of added significance in a black population in which skin pigmentation reduces the contribution of the cholecalciferol form to the total serum 1,25(OH)₂D value.¹⁵ The finding of a differential effect of vitamin D supplementation on 25(OH)D levels for the cases and the controls raises the issue of inclusion of such information in any study looking at the relationship between blood lead and vitamin D levels. The duration of lead toxic reactions, although not considered in this or other published studies, is another factor that will need to be considered in future prospective studies. Delineation of blood lead distribution will also allow easy comparison of results among studies.

The preliminary results showed no difference in bone mineralization for the cases and controls. This is not surprising and is consistent with results of other studies.⁴⁶

Although we did not explore all the psychosocial aspects that might lead to pica and elevated blood lead level, our study did show that the mean number of children per household for the cases was higher than for the controls and the level of maternal education was less than 12th grade for the cases and exceeded the 12th grade for the controls (Table 2). These differences did not reach statistical significance, but they suggest that the dynamics of a maternal-child interaction and the role of education merit further investigation. Our attempts to obtain environmental information (ie, fluorescent analyzer data, presence of chewable surfaces, and soil/dust analyses) yielded data that were, unfortunately, not useful.

Our secondary aim was to explore the relationship between calcium intake and pica score. We did not find any association between these two variables. Although animal studies have suggested that deficiencies in calcium intake may account for lead pica, the availability of lead, the presence of other nutritional deficiencies, and a prolongation of pica behavior even after correction of a deficiency (as is seen in animals) may make a simple correlation between lead pica and calcium intake difficult to demonstrate if, in fact, it exists.

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CONCLUSION

In this study of the relationship of three factors (blood lead level, calcium status, and behavior), a positive association between blood lead levels and a pica score was found. However, the cases and controls with high and low blood lead levels, respectively, could not be demonstrated to differ on four calcium measures. Likewise, calcium intake was not associated with pica scores. A history of pica, especially for paint chips, was the only significant factor found to differentiate between the groups. True primary prevention through detection of sources of lead,

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continued aggressive environmental intervention, and early identification of patients through screening remain the most effective means of dealing with lead toxic effects.

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Triage Decisions in Child Care for Sick Children

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• Child-care centers for children with mild, acute communicable, and noncommunicable illnesses are beginning to evolve. Few states have enacted regulations concerning the policies and procedures under which child-care centers for sick children operate. These centers should have policies regarding the triage and care of III children that promote the safety of all children and staff at the center. As part of the establishment of regulations for the Michigan Department of Social Services, Lansing, a triage model has been developed that provides a means of standardizing the screening process used to admit mildly ill children to such centers. We present pilot guidelines for use by center personnel, discuss considerations inherent in formulating triage policy for child-care centers for sick children, and provide a starting point for those attempting to standardize regulations governing child-care centers for sick children.

(AJDC. 1990;144:190-196)

The provision of adequate child care for children is an issue of increasing importance to parents, physicians, and social scientists. Interest in one aspect of this question, the provision of child care for children with mild acute illnesses, has become heightened. Proposals to create such centers in various states have made evident the need for the development of rules and regulations for the operation of such centers. We present guidelines suitable for use by sick child-care centers to determine which children may be admitted to or excluded

from such centers.

In 1987, approximately 50% of married mothers of children less than 1 year old and 60% of all mothers of children between 3 and 5 years of age were in the work force.1,2 Seventeen percent of children under 3 years old and 60% of children between 3 and 6 years of age received care outside the home.3 While the debate regarding the benefits and risks of the placement of young children in child care continues, many families choose to use child care for a variety of reasons. Child care is now being considered both as an employment benefit and an important component of government-sponsored employment programs.

Even the most stable child-care arrangements can be altered when the child becomes acutely ill. In the first 3 years of life, children may have 7 to 10 acute respiratory illnesses per year alone, and child-care centers often exclude sick children for part or all of each illness.3,4 Parents are then forced to choose other, possibly less satisfactory, arrangements for child care or to be absent from work. Even the most tolerant employer may find a series of unpredicted employee absences difficult to accept. One 1980 study found that 61% of employee absenteeism was due to unmet child-care needs, particularly those of sick children.5 In more restrictive job situations, the parent who frequently misses work because of the need to care for a mildly ill child may forfeit his or her job. Nationally, the total estimated cost of absenteeism and unemployment from this source alone is a major concern to employers.4 Few statistics concerning employers' policies and procedures regarding employee absence to care for sick children are available. In one survey, smaller companies were found to

be more flexible with their employees' absences than were larger companies.

Whether a parent should remain with the sick child, particularly for the first 1 or 2 days of illness, is an issue on which opinions vary. Nevertheless, when a child is excluded from usual child care because of illness, parents who feel they cannot be absent from work will seek another source of care. The nature and quality of these arrangements have been reviewed, and those that occur outside of established centers are not subject to the usual rules and regulations designed for the protection of children. ⁶

The issues surrounding the provision of child care for children with chronic health problems, including those who are dependent on technological support, are more complex. These children may require a more sophisticated level of care on a continuing basis, or they may be in regular child care but be excluded during an acute illness or exacerbation of their chronic condition. Parents of such children may have a greater need for the availability of child care because without it they may miss a significant amount of work or be unable to work at all. Centers designed to serve children with special health care needs have unique staffing, equipment, and physical plant requirements and therefore may need additional policies and procedures.

CHILD CARE FOR SICK CHILDREN

Child-care centers for children with mild acute communicable and noncommunicable illnesses are beginning to evolve. For sick children who cannot be at home, these centers presumably provide a safe environment conducive to the child's recovery. To date, few studies have examined the question of cross-

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contamination in such centers. In one such study, the relative risk of acquiring an upper-respiratory illness, a gastrointestinal illness, or varicella from children attending a sick child-care center was not significantly increased when compared with that of matched unexposed children. Child-care centers for sick children may serve also to protect some of the child's usual child-care companions from exposure to certain contagious illnesses. It should be noted, however, that the majority of childhood infections are caused by viruses and, with most viral infections, the period of contagion begins before actual symptoms of active illness.

Several different examples currently exist for the provision of child care for sick children. Care for mildly ill children may be provided in a separate section of a well child-care center that cares only for its own enrollees when they become sick. Some centers have developed arrangements to admit sick children from one or more other well child-care centers.* Free-standing centers designed solely as a temporary child-care source for sick children exist. 6 Some child care for sick children is also being performed in hospitals, sometimes on an existing pediatric ward. In 1986, it was estimated that more than 30 child-care centers for sick children were or had been in operation. 6 According to the National Association for Sick Child Daycare, although the exact figure is not entirely known, the number of such centers nationwide now exceeds 50 (personal communication, Gayle Gonzales, vice president, National Association for Sick Child Daycare, Foster City, Calif, January 1989). The American Academy of Pediatrics and the American Public Health Association have recently convened a series of expert panels to develop proposed national performance standards for out-of-home child-care programs.9 To date, however, few states have enacted regulations concerning the policies and procedures under which child-care centers that care for sick children should operate.

TRIAGE DECISIONS IN SICK CHILD CARE

In anticipation of requests to establish and operate child-care centers for sick children, the Michigan Department of Social Services has been developing rules and regulations for such centers (Task Force for the Care of Mildly Ill Children in Child Care Centers, Division of Child Day Care Licensing, Michigan Department of Social Services). The process of developing these rules and regulations has made evident the need for a method of triage to decide what types of childhood illnesses can be admitted to sick child-care centers. The method of triage involves developing criteria that provide a means of standardizing the screening process in a way that promotes the safety of all individuals concerned.

The triage of children seeking admission to sick child-care centers has several inherent considerations. The most apparent questions are when, who, and what: when will the triage decision be made, who will make it, and what admission criteria will be used?

The time when the decision is made about admission to a sick child-care center is complicated by several factors. If a child has been at home for 1 or more days, arrangements may be made with a center in advance of the day of admission. This allows a careful consideration of the child's situation. When the onset of illness is sudden, however, the parent may call in the morning or during the day seeking immediate admission. In this case, the need of the parent to arrive at work as soon as possible must be balanced with the safety of the sick child and the safety of others in the center. Policies and procedures regarding advance vs same-day admission should receive careful consideration by each center. Preregistration of the child at the sick child-care center many simplify this task.

Who will make the triage decision is the second important issue. Theoretically, the highest degree of safety could be produced by physician evaluation in each case. The on-site availability of a physician for this purpose would be efficient for parents but would be a significant expense for the centers and, ultimately, the consumer. At the opposite end of the spectrum, a policy of blanket admittance of all children or the use of untrained and inexperienced personnel for screening would fail to protect the child as well as other adults and children in that center. The on-site availability of

a licensed nursing professional experienced in children's illnesses to make triage decisions is a medically appropriate solution. This plan is also financially feasible since one or more such trained individuals should be directly involved in the provision of sick care in the center. The success of such a plan is highly dependent on the integrity and skill of both the parents and the individual who evaluates the information about the child's condition.

Contact with a physician, preferably the child's physician, either by telephone or in person before admission to a child-care center for sick children would seem to be a reasonable expectation for all but the mildest of illnesses. Physicians who feel uncomfortable making this decision on the basis of a telephone contact may elect not to render an opinion unless the child is examined. Children with certain potentially serious conditions should be seen by the physician and, if judged to have a serious illness, not admitted to a child-care facility. This policy of excluding seriously ill children from child care is consistent with the position of the American Academy of Pediatrics, Committee on Day Care.10

What format will be used to make decisions regarding admission to or exclusion from the sick child—care center? If nonphysician center personnel are to assume the initial triage role, they must have available to them criteria that are clear, comprehensive, reasonable, and efficient. The guidelines presented below represent a model for making determinations of this nature.

THE TRIAGE GUIDELINES

The triage guidelines presented in Tables 1 and 2 were developed by us as part of the development of rules and regulations that are currently being used in a pilot sick child—care center program in Kalamazoo, Mich. Certain illnesses listed in these tables do not necessarily require exclusion from regular child-care centers for medical reasons. However, since grounds for the exclusion of ill children vary among well child—care centers, a comprehensive list was developed.

Table 1 contains guidelines for the screening of children who are without an established diagnosis. These guide-

Clana as Currente*	Physician Evaluation Needed†	Later Physician Evaluation Needed If
Signs or Symptoms*	Yes	-, - <u></u>
Burns	tes .	Condition worsens, eg, increasing pain, redness, purulent drainage
Cold (upper-respiratory infection) <3 mo old	Yes	Condition worsens, eg, persistent fever, breathing difficulty
> 3 mo old with/without fever	No	Same
With foul-smelling or purulent nasal discharge	Yes	Same
Cold sores Alone	No	Condition worsens, eg, vomiting, fever, refusal to eat
With vomiting, fever, or refusal to eat	Yes	Existing signs/symptoms worsen
Conjunctivitis or "pink eye" White of eye and inner eyelid become red or pink with/without clear or yellow drainage	Yes	Condition worsens, eg, pain, redness, redness spreads beyond eyelid
Cough Cough alone (in child who seems well)	No	Condition worsens, eg, pain, difficult or fast breathing, blood in sputum, wheezing
<2 y old with fever	Yes	Same, plus persistent fever
>2 y old		
With fever <48 h only	No	Same
With fever >48 h	Yes	Same
With pain, difficult or fast breathing, blood in sputum, wheezing	Yes	Existing signs/symptoms worsen
Cuts/bruises If admission sought for single or multiple bruises/cuts with/without limitation of activity	Yes .	Increasing pain, redness, swelling, drainage
Dental procedures	No; however, dental evaluation needed	Increasing pain, bleeding, fever
Diarrhea If > 48 h	Yes	Condition worsens, eg, vomiting, blood or mucus in stools, dehydration, change in alertness or behavior
If dehydration (sunken eyes, dry mouth, or no voiding in past 8 h)	Yes	Same
If blood or mucus in stool	Yes	Same
If vomiting	Yes	Same
If <48 h with no dehydration, blood or mucus in stools, and without vomiting	No .	Same
Difficulty breathing	Yes	Condition worsens, eg, wheezing, increased shortness of breath, cyanosis
Ear pain	Yes	Increasing ear pain, fever, discharge, lethargy, headache
Fever Temperature >38.4°C (>101°F) alone, for >24 h	Yes	Condition worsens, eg, cough, diarrhea, vomiting, change in alertness or behavior, other symptoms/ signs
Any rectal temperature >38.4°C in child <3 mo old	Yes	Same
Temperature <38.4°C for <24 h in child >3 mo old	No	Same
Temperature >38.4°C with other signs/ symptoms	(see elsewhere on Table [.] Yes	1 under appropriate signs/symptoms, otherwise) Same
teadache <48 h, no other symptoms	No	Headache ≥48 h, vomiting, fever, change in alertness or behavior
≥ 48 h, no other symptoms	Yes	Vomiting, fever, change in alertness or behavior
If severe with vomiting and/or change in alertness or behavior	Yes	Existing signs/symptoms worsen
lead injury	Yes	New/increasing pain, change in behavior or alertness
lives	Yes	More rash, problems breathing
		•

Table 1.—Guidelines for Triage Decisions for Children Without Established Diagnosis* (cont)				
Signs or Symptoms*	Physician Evaluation Needed†	Later Physician Evaluation Needed If		
Jaundice Yellow skin or eyes	Yes	Condition worsens, eg, vomiting, diarrhea, fever, change in alertness or behavior		
Lice	Yes			
Nausea/vomiting <24 h without diarrhea or dehydration in child >6 mo old	No	Condition worsens, eg, continuous vomiting, dehydration, blood or bile in vomitus, change in alertness or behavior		
<24 h with diarrhea	Yes	See diarrhea (above)		
>24 h	Yes	Condition worsens (as above)		
With head njury	Yes	Same		
With change in consciousness	Yes	Same		
Continuous vomiting, dehydration, blood or bile in vomitus, change in alertness or behavior, or child <6 mo old	Yes	Existing signs/symptoms worsen		
Oral lesions Canker sores, thrush, cold sores (alone)	No	Condition worsens, eg, refusal to eat, vomiting, or fever		
All oral lesions with refusal to eat, vomiting, or fever	Yes	Existing signs/symptoms worsen		
Pain, swelling, or lack of movement in extremity	Yes	Existing signs/symptoms worsen		
Painful urination	Yes	Worsening/persistent fever, discomfort, blood in urine		
Pinworms	Yes			
Rash With fever	Yes	Condition worsens, eg, rash spreading, difficult breathing, vomiting, change in alertness or behavior		
Without fever	Yes	Same		
Diaper rash	No	Pain, bleeding, change in character of rash (pustules)		
Chronic or recurring rash without fever	No	Worsening of rash		
Seizures Undiagnosed	Yes	Condition worsens, eg, increased seizure activity, change in alertness or behavior		
Skin infection Any	Yes	Condition worsens, eg, purulent discharge, spreading lesions, redness, or pain		
Sore throat <2 y, without fever	No	Development of fever, pain, refusal to eat		
>2 y, without fever	Yes	Same		
With fever	Yes	Increasing fever, pain, refusal to eat		
Teething	No	***		
Wheezing	Yes	Condition worsens, eg, increased wheezing, breathing difficulty, cyanosis		
Recovery from major surgery/major illness		Advanced-level care with explicit physician instruction and ongoing supervision; facility must be able to provide appropriate care		
Technological dependence (Ventilator dependence, peritoneal dialysis, tracheostcmy, etc)		Advanced-level care with explicit physician instruction and ongoing supervision; facility must be able to provide appropriate care		
Immune system deficiencies	Children with primary or acquired deficiencies of the immune system (AIDS, children taking immunosuppressive medication, hypogammaglobulinemia) may be at increased risk if placed in child-care center for sick children; child's parents and center personnel should be fully aware of this risk, and physician approval must be sought for placement in facility			

^{*}In these guidelines, fever refers to an oral or rectal temperature above 38.4°C. Axillary temperatures may be lower than rectal temperatures by 0.28°C.13 AIDS indicates acquired immunodeficiency syndrome.

†Type of evaluation at physician's discretion.

lines are organized by signs, symptoms, or major complaints as they would be presented by the parent. For certain conditions, those judged to be more serious, some type of physician evaluation

is suggested, and Table 1 provides guidelines to determine if a child needs to be evaluated or reevaluated by his or her physician. Table 2 contains guidelines for admission, exclusion, and reevaluation of children for whom a diagnosis has been established. The guidelines are designed for use by nursing professionals in the context of each center's staff and physical resources.

Diagnosis/Evaluation				
(With or Without Treatment)	Exclusion or Admission†	Reevaluation After Admission If		
Asthma	Admit with A	Wheezing worsens, breathing difficulty, cyanosis		
Conjunctivitis				
(pink eye)	Admit after treatment is initiated with A and B	Pain, redness extends beyond eyelid, increasing discharge		
Dental procedures	Admit with instructions provided by dentist	Increasing pain, fever, bleeding		
Diarrhea Acute gastroenteritis (presumed viral)	Admit with A	Diarrhea >48 h, dehydration, blood or mucus in stoo		
Campylobacter	Admit after treatment is initiated for 2 d or diarrhea has subsided and A and B; then attempt to return to usual child care	Diarrhea worsens or resumes, vomiting, dehydration		
Giardiasis	Admit after treatment is initiated and A and B; or ce child is asymptomatic, attempt to return to usual child care	Same		
Salmonella	Exclude until diarrhea resolves, admit if child cannot return to usual child care	Same		
Shigella	Exclude until 3 negative stool cultures; then admit if child cannot return to usual care	Same .		
Other	Admit with A .	Same		
Ear infection Otitis media	Admit with A	Increasing pain, discharge, fever, headache, lethargy		
Otitis externa	Admit with A	Increasing pain, discharge, fever		
Head injury				
Postconcussion	Admit with written A and B	New/increasing pain, change in alertness or behavior		
Skull fracture	Admit with written A and B	Same		
Hives Allergic reaction	Admit with A	Increas ng rash, wheezing, difficulty breathing		
Jaundice Hepatitis A	Exclude			
Hepatitis B	Admit with written A and B	Existing signs/symptoms increase		
Hepatitis B carrier	Attempt to return to regular child care; if not, admit with written A	Same		
Other	Admit with A and B	Same		
Limb injury				
• Sprain	Admit with A and B	Increasing pain, swelling		
Muscle strain	Same	Same		
Bone fracture	Same	Same		
Other injury	Same	Same		
Minor surgery Minor skin surgery, ear ventilation tubes, myringotomy	Admit with A and B	Fever, increasing pain, red or swollen ear or surgery site		
Nausea/vomiting	See acute gastroenteritis (above)	•••		
Oral lesions Aphthous ulcers (canker sores)	Admit	Existing signs/symptoms worsen, refusal to eat, vomiting		
Candida (oral thrush)	Admit with A	Same		
Herpes stomatitis	Admit with A	Same		
Pinworms	Admit after treatment initiated and with A	•••		
Rash		,		
Measles, rubella, mumps, varicella (chickenpox)	Exclude unless center specifically equipped and approved to provide isolation care; otherwise, admit after period of communicability	Change in alertness or behavior, breathing difficulty, vomiting, decreased fluid intake		
Lice, scabies, ringworm	Admit after treatment initiated	Worsening rash		

Table 2.—Guidelines for Triage Decisions for Children With Established Diagnosis* (cont)				
Diagnosis/Evaluation (With or Without Treatment)	Exclusion or Admission†	Reevaluation After Admission if		
Fifth disease	Admit, but may wish to exclude for protection of staff	Same		
Kawasaki disease	Admit with A and B	Same		
Respiratory infection Bronchiolitis	Exclude RSV + children if caring for infants <3 mo or children <2 y old with chronic lung or heart disease; otherwise, admit with A and B	Existing signs/symptoms worsen		
Bronchitis	Admit with A and B	Pain, difficult or fast breathing, blood in sputum, wheezing, cyanosis		
Croup	Admit with A and B	Existing signs/symptoms worsen		
Pertussis	Exclude for 5 d after erythromycin therapy beings; A and B	Pain, difficult or fast breathing, blood in sputum, wheezing, cyanosis		
Pneumonia	Exclude for 24 h, then A and B	Same		
Tuberculosis	Admit after initiation of treatment (if unable to return to usual child care); written A and B	Same		
Salmonella carrier	Attempt to return to usual child care; if not, admit temporarily with A			
Seizures Seizure disorder	Admit with A and B	Increased seizure activity, change in alertness or behavior		
Febrile seizures	Admit with A and B	Same		
Skin infections Impetigo	Admit after treatment initiated and A	Lesions spreading		
Other	Same	Purulent discharge, spreading lesions or redness, pain, etc		
Sore throat Streptococcal pharyngitis	Admit after treatment initiated for 24 h and A	Increasing fever, pain, refusal to eat		
Infectious mononucleosis	Admit with A and B	Increasing pain, refusal to eat		
Upper-respiratory infections Viral	Admit	Persistent fever, difficulty breathing		
Purulent rhinitis	Admit after antibiotic treatment initiated and A	Same		
Sinusitis	Same	Same		
Jrinary tract infection	Admit with A	Increasing/new fever, discomfort, blood in urine		
Recovery from major surgery/ major illness	Advanced-level care with explicit physician instruction and ongoing supervision; facility must be able to provide appropriate care			
fechnological dependence (ventilator dependence, peritoneal dialysis, trecheostomy, etc)	Advanced-level care with explicit physician instruction and ongoing supervision; facility must be able to provide appropriate care			
Immune system deficiencies		aglobulinemia) may be at increased risk if placed in child- and center personnel should be fully aware of this risk; and		

^{*}In these guidelines, fever refers to an oral or rectal temperature above 38.4°C. Axillary temperatures may be lower than rectal temperatures by 0.28°C.13 RSV + indicates positive for respiratory syncytial virus; AIDS, acquired immunodeficiency syndrome.

Several assumptions were made in the development of these guidelines. The first was that the safety of the sick child and others in the center must supercede the parental need to arrange care for the sick child or the financial needs of such a center. The second assumption was that a child may or may not have had contact with a physician immediately before the time the parent contacts the center for admission. For this reason, guidelines are needed for both situations. The third assumption was that all children admitted to the center under these guidelines will have been age-appropriately immunized, and routine tuberculin testing will have been conducted in accordance with recommendations by local public health officials.¹¹ Fourth, it was assumed that policies and procedures will exist in each

[†]A indicates physician instructions required (may be verbally relayed by parent unless otherwise noted); B, return with physician approval only (may be verbally relayed by parent unless otherwise noted).

center to minimize cross-contamination and protect children and staff as outlined in the Report of the Committee on Infectious Diseases of the American Academy of Pediatrics." The final assumption was that the medical condition of the children admitted will be appropriate to the level of care and supervision available in the center and that, subsequent to initial screening, continuing observation of the child's condition and decisions about the need for physician assessment are required of childcare center personnel.

GENERAL MEDICAL CONSIDERATIONS

Differentiation is made in these guidelines between noncommunicable and communicable conditions. If children with noncommunicable conditions such as recovery from burns, injuries, or surgery are admitted, the center must have the capacity to provide appropriate care and to limit the risk of acquiring illness from other admitted children. For communicable illnesses, the level of communicability should be considered. The admission of children with highly communicable illnesses such as chickenpox requires special permanent adaptations in the physical structure of the facility and appropriate staffing to provide separate care for these children. Centers that are not suitable for these tasks should automatically exclude children with these type of illnesses. Centers should consider whether they wish to admit children with other illnesses known to spread rapidly through child-care centers such as hepatitis A, respiratory syncytial virus, and Shigella. Center administrators should seek the advice of local public health officials where concerns or conflicts arise.

In Table 1, for each sign or symptom, guidelines are provided concerning whether physician advice or evaluation is necessary. The term evaluation means that a physician, chosen by the family, is contacted to evaluate the child's illness and the kind of care needed. Whether that evaluation is conducted in person or by telephone is assumed to be at the physician's discretion. In general, these guidelines reflect that the younger the infant or the more serious the sign or symptom is, the more important is it that physician evaluation

be sought. Since temperature response to antipyretics has not been shown to be a useful indicator with which to differentiate the causes of febrile illness in children, careful monitoring of the febrile child's condition is essential. 12 While the majority of children experiencing a cold, cough, diarrhea, fever, nausea, vomiting, rash, or sore throat have selflimited viral illnesses, physician advice or evaluation may serve to assist identification of those children with a more serious infectious process. In children presenting to the center with acute injuries such as burns, fractures, contusions, or lacerations, physician evaluation should normally include a careful consideration of nonaccidental causes.

In Table 2, for those infections for which specific outpatient antimicrobial therapy is available and appropriate. the length of exclusion from child-care centers follows recommendations made by the American Academy of Pediatrics, Committee on Infectious Disease.10 Table 2 also indicates whether physician approval, specific instructions for care. ar both should be required for entry to the child-care center for sick children. In both Tables 1 and 2, examples of reasons for physician evaluation or reevaluation after admission to the center are provided to guide center staff to identify those children who are becoming more ill. These examples are not meant to be all-inclusive since the provision of such a list for each sign, symptom, and diagnosis would be prohibi-

SPECIAL MEDICAL CONSIDERATIONS

Children with physical handicaps and chronic illnesses represent a special group in child care. The majority of these children are able to function in a usual child-care center, but acute illnesses or acute exacerbations of their chronic illnesses may require care in a center equipped to serve their needs. Children who are medically fragile or who require continuing care and supervision should be placed only in a center prepared to provide such service. The need for such facilities exists, and centers to serve this population are beginning to be developed. The guidelines presented in this article will need to be adapted to meet the needs of this population. Children with primary or acquired deficiencies of the immune system (children with acquired immunodeficiency syndrome, hypogammaglobulinemia, or children taking immunosuppressive medication) may be at increased risk if placed in a child-care center for sick children. Parents and center personnel should be fully aware of this risk, and physician approval must be sought before placement of such a child in a sick child-care facility.

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Breath Hydrogen Excretion in the Premature Neonate

Henry W. Cheu, MD, David R. Brown, MD

 We measured breath hydrogen excretion in 103 neonates from birth to as late as 2 months of age. The patients weighed less than 2000 g at birth and were part of a study of hydrogen excretion as a screening test for necrotizing enterocolltis. Hydrogen excretion in parts per million was normalized for the quality of the expired air by dividing by the Pco, of the gas sample. The rise in the H₂/CO₂ ratio was influenced by gestational age, energy intake, and antibiotic usage but not by the daily frequency of feeding. The mean \pm SD peak H_a/CO_a ratio was 5.1 \pm 3.6 ppm per millimeter of mercury and occurred at 16.0 ± 11.0 days of age. The age at which the peak H₂/CO₂ occurred varied with gestational age. Patients born between 23 and 28 weeks gestational age (n=34) were 22.9 ± 13.1 days of age when they experienced their peak H2/CO2 ratio, whereas those born between 29 and 34 weeks gestational age (n = 62) were 12.2 ± 7.5 days of age. The age at which the peak H₂/CO₂ ratio occurred did not differ between these two groups when corrected for the age at which oral intake exceeded 420 kJ/kg per day. These results suggest that premature neonates require experience with ingesting more than 420 kJ/kg per day before bacteria and carbohydrates are present in large enough quantities to permit measurable hydrogen production. This information will be useful in future studies of premature gut development and physiology and in studying pathologic processes in which malabsorption may play a role.

(AJDC. 1990;144:197-202)

Breath hydrogen excretion has been used for a number of years to diagnose malabsorption and bacterial overgrowth syndromes in adults and children. ¹³ This test has been adapted for

use in neonates, 2,4,5 and recent reports have demonstrated an increase in breath hydrogen excretion 24 hours prior to the onset of clinical necrotizing enterocolitis. 6,7 Breath hydrogen excretion has also been suggested as a test for malabsorption in premature neonates with short-gut syndrome.8 While some data have been reported on hydrogen excretion in premature neonates, 5,9-11 there are no reports of hydrogen excretion results from daily testing in a large group of these patients. Detailed information on breath hydrogen excretion in the healthy premature neonate would be useful in the study of normal and pathologic gut function.

We report herein the results of our daily measurements of breath hydrogen excretion in a population of premature neonates. This report relates hydrogen excretion to feeding, antibiotic exposure, age, and gestational age (GA) and thereby establishes norms for breath hydrogen excretion in this population during the neonatal period.

PATIENTS AND METHODS

All neonates admitted to the neonatal intensive care unit of Magee-Womens Hospital, Pittsburgh, Pa, during the 9 months from September 1986 through May 1987 who weighed less than 2000 g at birth were eligible for the study. If parental permission was given, daily breath hydrogen measurements were begun as early as the first day of life and continued for a variable period that extended to 2 months of age in some patients. Seventytwo percent of the eligible infants admitted to the neonatal intensive care unit during this period were included in the study. The reasons for exclusion were lack of parental consent, necrotizing enterocolitis, GA of greater than 34 weeks at birth, or no studies performed before 10 days of age.

A modification of the technique of Maffei et al⁴ was used. For infants who had an endotracheal tube in place, gas samples were collected through a modified endotracheal tube adapter that allowed one person to collect

exhaled gas in a syringe while another provided respiratory assistance for the patient by hand at a rate and pressure that simulated that of the respirator. If the patient was not breathing with respirator assistance, a feeding tube (3.5F or 5F, Sherwood Medical, St Louis. Mo) was inserted through the nose into the hypopharynx, and exhaled gas was collected by coordinating withdrawal with the patient's exhalations. A 60-mL syringe (Becton-Dickinson, Rutherford, NJ) with an attached three-way stopcock (Burron Medical, Bethlehem, Pa) was used to collect and store the specimens at room temperature. All specimens were analyzed in duplicate within 12 hours of collection. Previous testing using known concentrations of gas had demonstrated the stability of the storage system for as long as 72 hours. The hydrogen level was measured using a Quintron 12A gas chromatograph (Quintron, Milwaukee, Wis). 12 The chromatograph has a sensitivity of less than 3 ppm and an accuracy to within 3 ppm and was calibrated daily using a standard of known concentration. All specimens from each day were run in the hour after calibration, and calibration was repeated after every 20 samples. The PCO, was measured on a carbon dioxide monitor (Puritan-Bennett, Kansas City, Mo). Samples were collected daily without regard to feedings, since preliminary studies of 10 infants tested every half hour through several feeding cycles showed no significant variation due to feeding. The type and amount of feeding and details of antibiotic therapy were recorded daily.

The investigators were not involved in the care of the infants and did not influence their nutritional management. All infants were fed formula in which lactose was the only sugar source. Seventy percent of the infants were fed formula with 2.8 kJ/mL, and the remainder were fed human milk or human milk supplemented with formula with either 2.8 or 3.4 kJ/mL. All feedings were intermittent, every 2 or every 3 hours. More than 70% of the specimens were obtained by one of us (H.W.C.). The remainder were obtained by nurses who had been trained in the technique. Specimens with a PCO, lower than 10 mm Hg were considered inadequate; either they were discarded or a new specimen was obtained.

Data were analyzed using the t test, χ^2

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test, analysis of covariance, 18 or a test for differences between survival curves. 14,16

RESULTS

A total of 1990 specimens were obtained from 103 patients who weighed 1.30 ± 0.38 kg (mean \pm SD) and were born at 29.5 ± 2.8 weeks' gestation. For the purpose of the statistical analysis, two gestational groups were created by dividing the patients into those whose GA was 23 to 28 weeks (n=40; mean GA, 26.5 ± 1.5 weeks; mean birth weight, 0.96 ± 0.21 kg) and those whose GA was 29 to 34 weeks (n=63; mean GA, 31.4 ± 1.4 weeks; mean birth weight, 1.53 ± 0.29 kg).

0 = No and 1 = Xes for Antibiotic Use (Diamonds)

All breath hydrogen values were divided by the Pco, of the sample as a means of standardizing for the quality of the expired gas. 6,7,9,16,17 The Pco, and hydrogen values of sequential specimens taken from the same subject at 10-minute intervals over a 90-minute period by the same experimenter showed a mean coefficient of variation of 28.2% for Pco. and 30.2% for hydrogen for the five patients who were tested and had hydrogen values exceeding 5 ppm. The average coefficient of variation for the ratios. of H,/Pco, from these same patients was only 8.3%. Thus, all results are presented as H₂/Pco₂ ratios. mean \pm SD peak ratio was 5.1 ± 3.6 for all 103 patients and did not differ between the two GA groups. The mean ± SD age at which this peak occurred was 16.0 ± 11.0 days.

Infants did not excrete hydrogen until a variable number of days after their feedings were begun. Antibiotics, usually ampicillin and kanamycin, were given to many infants for a brief period, usually during the first week of life. Representative hydrogen excretion patterns for two neonates are shown in Fig 1. Feeding and antibiotic data are presented along with the simultaneously obtained H₂/CO₂ ratios. Data in Fig 1 are from a patient born at 33 weeks GA (top) and one born at 28 weeks GA (bottom). A number of characteristic features are illustrated in this figure. Hydrogen excretion occurred only after feedings of 420 kJ/kg per day had been established for a number of days, in this case for 3 (top) and 7 (bottom) days. The more premature neonate (bottom) was older than the more

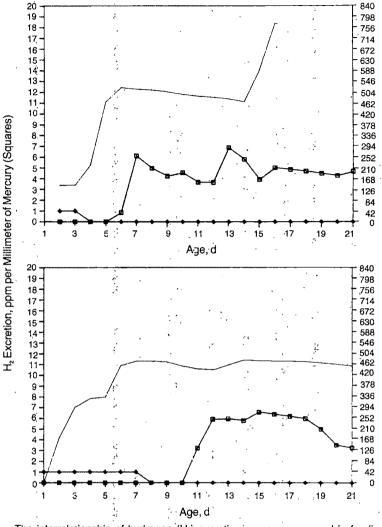


Fig. 1.—The interrelationship of hydrogen (H_2) excretion, energy consumed in feeding, and antibiotic use. Each graph summarizes data from a single patient.

mature neonate when hydrogen excretion began (11 vs 7 days). Finally, the initial rise in the $\rm H_2/CO_2$ excretion ratio was rapid and persistent. The close relationship of hydrogen excretion and feedings is illustrated in Fig 2. These data are from a patient who had feedings withheld from days 11 through 17. Hydrogen excretion dropped to 0 during this period and then promptly returned to previous levels with the reinstitution of feeding.

Some features of hydrogen excretion suggested by these individual patient data can be better illustrated with group data. Figure 3 shows the sharp rise and subsequent plateau in hydrogen excretion in relation to feeding for all patients who experienced an ordered change in the H₂/CO₂ ratio from less

than 2.0 to greater than 2.0 during the time they were studied. Seventy-nine of the 103 patients met this criterion. The mean values for feeding and the $\rm H_2/CO_2$ ratio are shown on successive days; day 0 was the day on which the $\rm H_2/CO_2$ ratio was first greater than 2.0. Feedings also exceeded a mean of 420 kJ/kg per day for the first time on day 0. Figure 3 also shows the total number of observations that contributed to each of the 29 data points on each curve.

Since feeding may be related to either GA or postnatal age or both, the relationship of hydrogen excretion to feeding was also explored in relation to these factors. The relationship of hydrogen excretion to GA is summarized in Fig 4, which shows the mean H₂/CO₂ ratio for each day during the neonatal period for

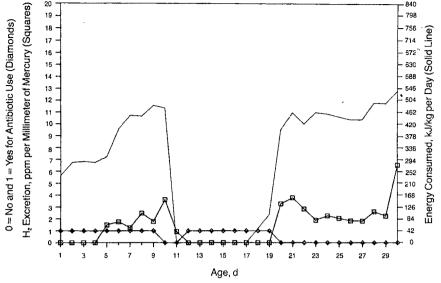


Fig 2.—The effect of withdrawing feedings. The data are from a single patient.

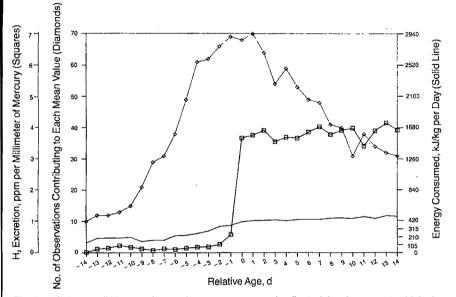


Fig 3.—Hydrogen (H_2) excretion and energy consumed adjusted for the age at which the H_2/CO_2 ratio first exceeded 2.0. Day 0 is the first day this ratio was exceeded. The data are from 79 patients.

the two GA groups. Patients born between 23 and 28 weeks GA (n=34) were 22.9 ± 13.1 days of age when their highest H_2/CO_2 ratio was measured, whereas those born between 29 and 34 weeks GA (n=62) were 12.2 ± 7.5 days of age (P<.001). Since there are different numbers of observations per day contributing to each of the 28 mean values in each group, a straightforward statistical comparison of the two groups is not possible. However, if the data are plotted as survival data (Fig 5), where sur-

vival is defined as maintaining an $\rm H_2/CO_2$ ratio lower than 2.1, the two groups can be shown to be different in the rate at which they exceed this value (0.0449 vs 0.087 patients per day, z=2.86, P<.01). There was also a statistically significant negative correlation between the age at which the $\rm H_2/CO_2$ ratio first exceeded 2.0 (the dependent variable) and GA (r=-.5349, P<.001, y=51.75-1.39x).

This apparent GA difference could be accounted for by the rate at which feed-

ings were established. When the data shown in Fig 4 are adjusted for the age at which the patient was consuming more than 420 kJ/kg per day (Fig 6), the apparent effect of GA on hydrogen excretion disappears. The effect of feedings on hydrogen excretion can be further highlighted by the statistically significant positive correlation between the age when the patient first consumed more than 420 kJ/kg per day (the independent variable) and the age at which the $\rm H_2/CO_2$ ratio first exceeded 2.0 (r=.5037, P<.001, y=0.55x+4.71).

When the relative importance of the association of these two factors with hydrogen excretion is examined by analysis of covariance, there is little to choose between them (Table). Approximately 25% of the total variance in hydrogen excretion can be accounted for by either factor, and an additional 8% can then be accounted for by the remaining factor. The decreased number of patients included in these analyses is the result of some patients failing to meet one or both of the conditional requirements for inclusion (ie, not increasing the H₂/CO₂ ratio to more than 2.0 or not having data available from the time before feedings first exceeded 420 kJ/kg per day).

The influence of antibiotic use on the H/CO, ratio was impossible to separate completely from age using these data. If hydrogen excretion data for the last 3 days the patient received antibiotics are compared with hydrogen excretion data for the first 3 days not receiving antibiotics, the H₂/CO₂ ratio was significantly greater while patients were not receiving antibiotics: 0.16 ± 0.34 for patients with a GA of 23 to 28 weeks (paired t = 2.53, P < .05) and 1.01 ± 1.68 for patients with a GA of 29 to 34 weeks (paired t = 3.90, P < .01). However, this effect also included a strong influence of postnatal age, a factor confounded with antibiotic use and feeding experience. When survival curves are compared after the data have been adjusted for antibiotic use (Fig 7), there is still a strong GA effect (z=2.46, P<.05), indicating that antibiotic use did not account for all of this difference in the H2/CO2 ratio.

COMMENT

Studies in adults have shown that hydrogen production in the gut is highly correlated with hydrogen excretion in

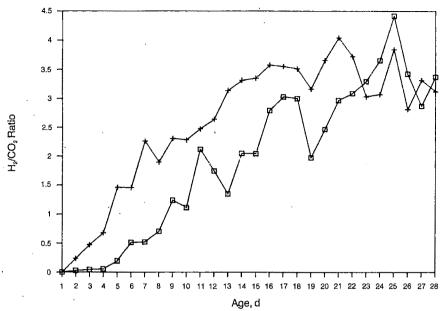


Fig 4.—The effect of gestational age on hydrogen (H₂) excretion. Squares represent infants with a gestational age of 23 to 28 weeks; plus signs, infants with a gestational age of 29 to 34 weeks.

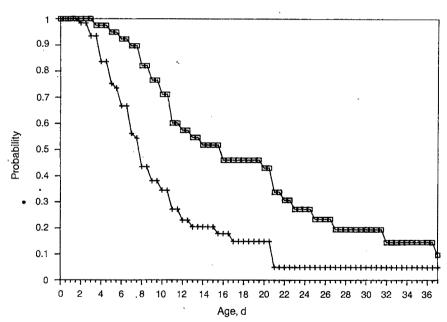


Fig 5.—Survival analysis for the age at which the H₂/CO₂ ratio first exceeded 2.0. Survival here is defined as maintaining an H₂/CO₂ ratio lower than 2.1. Squares represent infants with a gestational age of 23 to 28 weeks; plus signs, infants with a gestational age of 29 to 34 weeks.

expired air and that approximately 10% to 20% of the hydrogen produced is excreted via the lungs. In the adult human, hydrogen production depends on fermentable substances reaching the bacterial flora of the gut. Our data from neonates suggest a mechanism for hy-

drogen production similar to that seen in the adult human, although recently published data indicate that term neonates excrete nearly 50% of their hydrogen production via their lungs. ¹⁹

Infants in this study did not excrete hydrogen until several days after their

feedings were begun. This finding is consistent with recently published data showing that 7 of 22 neonates who were tested once during the first 6 weeks of life had no detectable breath hydrogen excretion.19 The interval between feeding and hydrogen excretion in our patients seemed to depend on the GA of the infant as well as the enteral energy intake. Once an infant began to produce hydrogen, there was a rapid rise in the amount of hydrogen produced. Thereafter, hydrogen excretion remained fairly constant unless feedings were interrupted, at which point hydrogen excretion promptly fell back to 0. Once feedings were resumed in an infant who had previously demonstrated hydrogen production, hydrogen excretion rapidly recurred without an appreciable lag period. A reasonable explanation for these observations is that the premature infant's gut is not yet colonized when feedings are begun. Some time after feedings are begun, the gut becomes colonized and hydrogen production begins. Once the gut is colonized, the excretion of hydrogen is dependent on the presence of substrate in the gastrointestinal tract.

The rapid rise in the rate of hydrogen excretion when hydrogen is first produced resembles a log growth curve. Stevenson et al¹⁰ showed in 12 premature infants that changes in hydrogen excretion correlated with changes in quantitative Enterobacteriaceae counts. Long and Swenson11 found that colonization with coliform bacteria had taken place in 77% to 86% of normal term infants by the time they were 4 to 8 days old. At 4 days of age, colonization with anaerobic bacteria had taken place in 96% of term infants compared with only 55% of preterm infants (mean GA, 34 weeks). Although we do not have data on gut colonization in our study patients, earlier reports show that gut colonization occurs at approximately the rate at which we observed the initiation of hydrogen excretion and occurs earlier in more mature neonates, as we observed with hydrogen excretion. This evidence suggests an association between hydrogen excretion and bacterial colonization.

Both bacteria and fermentable substrates must be present in the gastrointenstinal tract for bacterial fermen-

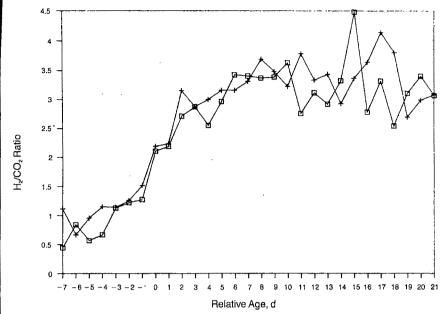


Fig 6.—Breath hydrogen excretion adjusted for feeding. Day 0 is the first day on which the energy consumed exceeded 420 kJ/kg per day. Squares represent infants with a gestational age of 23 to 28 weeks; plus signs, infants with a gestational age of 29 to 34 weeks.

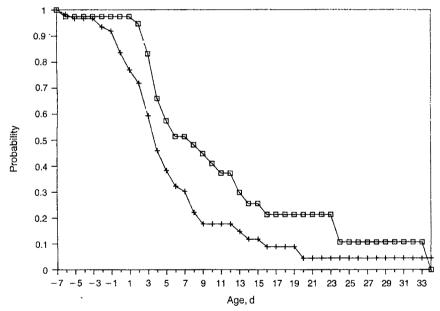


Fig 7.—Survival analysis for the age at which the $\rm H_2/CO_2$ ratio first exceeded 2.0. Day 0 is the first day without antibiotic treatment. *Survival* here is defined as maintaining an $\rm H_2/CO_2$ ratio lower than 2.1. Squares represent infants with a gestational age of 23 to 28 weeks; plus signs, infants with a gestational age of 29 to 34 weeks.

Regression Analysis Summary*							
Source	df SS		F	% of Variance			
Total	73	3302.595		100.0			
Regression on gestational age alone	1	819.136	26.32	24.8			
Regression on feeding after gestational age	1	273.462	8.79	8.3			
Regression on feeding alone	1	838.066	26.92	25.4			
Regression on gestational age after feeding	1	254.548	8.18	7.7			
Deviation	71	2209.988					

^{*}Analysis of covariance for the effects of gestational age and the age at which the patient was consuming more than 420 kJ/kg per day on the age at which the H₃/CO₂ ratio first exceeded 2.0.

tation to occur. All neonates, but especially premature neonates, absorb lactose poorly early in life. Since the neonatal gastrointestinal tract initially contains neither bacteria nor carbohydrate substrate, the delay we observed between the initiation of feeding and hydrogen excretion is compatible with the time required to have both factors present in sufficient quantity to produce fermentation. The close temporal relationship between consuming more than 420 kJ/kg per day and hydrogen excretion suggests that sufficient malabsorption does not occur until this quantity of feeding is achieved.

The lack of variation in breath hydrogen excretion within the daily feeding schedule in our population of premature neonates is of some interest. Full-term neonates have been reported to show variations in hydrogen excretion in relation to the time of feeding. However, others have shown that premature neonates do not show such variations. This discrepancy may be accounted for by the more frequent feedings given premature neonates, by differences in intestinal transit time, by variations in minute ventilation, or by some combination of these factors.

Our data on breath hydrogen excretion in the healthy premature neonate establish GA standards and show a relationship with feedings and, to a lesser extent, with parenteral antibiotic exposure. The measurement of breath hydrogen excretion in premature neonates has already found a role in the early diagnosis of necrotizing enterocolitis. 6,7 The availability of these standards for the healthy premature neonate offers the opportunity to use this relatively simple test to study pathologic processes such as necrotizing enterocolitis and malabsorption in greater detail as well as to investigate the normal development of bacterial colonization and carbohydrate absorption.

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Book Review

Fetal Neurology, International Review of Child Neurology series, edited by A. Hill and J. J. Volpe, 317 pp, \$69, New York, NY, Raven Press, 1989.

One might ask, "What are neurologists doing in a place like this?" in relation to a book on fetal medicine. However, as the editors noted in their preface, the field of neonatal neurology has expanded so much in the past decade that it is only natural that interest in fetal neurology would follow. Clearly, early fetal development is the "money area" where the foundations of all subsequent neurological integrity are laid. Also, with increasing knowledge that intrapartum events are far less important than earlier events in producing the unholy trinity of mental retardation, cerebral palsy, and epilepsy, neurological research and clinical efforts have logically turned toward the prenatal period to help increase our understanding of congenital neurological disorders in children.

This text, the fifth volume in the International Review of Child Neurology series, the official publications of the International Child Neurology Association, is divided into three major broad areas: antepartum fetal assessment, intrapartum fetal assessment, and major specific fetal conditions. Fetal behavior and movement, antepartum fetal monitoring, and responses to stimulation are reviewed. Some amazing sonograms in the chapter on fetal neuro-ophthalmology illustrate ocular size, morphology, fetal eye movements, and even the measurement of pupillary size in utero.

Nonstress and contraction stress tests are reviewed in the second major section of the book. The editors note that the neurophysiologic mechanisms responsible for fetal heart rate accelerations in response to fetal movements are still not completely understood. Both tests are still imperfect, with the contraction stress tests having a large false-positive rate (25%). The determination of a fetal biophysical profile score is reviewed as a means of surveillance of fetal well-being; unfortunately, however, this test has a false-positive rate of 43%. The biophysical profile score includes assessment of fetal body movements, tone, fetal heart rate, and amniotic fluid volume in addition to the nonstress test and placental grading.

Doppler ultrasound study of fetal-placental and utero-

placental circulations are reviewed in chapter 7. The studies have major relevance to fetal compromise as intrauterine growth retardation, as well as assisting in tl study of fetal cerebral blood flow. Preliminary eviden suggests that blood flow changes may serve as an ear warning signal of impending asphyxia.

The subjects of fetal distress and fetal monitoring a reviewed in detail. The authors note that abnormal fet heart rate tracings do not correlate well with outcome as must not be used to infer fetal "asphyxia" or brain damag The editors stress, as have others in recent years (Freems J, Nelson K. Intrapartum asphyxia and cerebral pals *Pediatrics*. 1988;82:240), that neurologic sequelae of h poxic-ischemic encephalopathy cannot be said to have occurred unless there were identifiable signs of enceph lopathy in the neonatal period.

The final section is a review of neurosurgery of the fetu including fetal hydrocephalus and spina bifida. Appropria caveats are noted with regard to shunt surgery for hydr cephalus and subsequent intellectual outcome. Other alternatives such as transabdominal cephalocentesis are note Finally, an elegant chapter by Jacob and Sarnat is a review of the influence of the brain on normal and abnormal must development. It was previously thought that "never the twain shall meet," but it is clear that congenital myopathin in some cases may represent an expression of underlying central nervous system disease.

Fetal Neurology serves as an exciting bridge between the advances of neonatal neurology in recent years and the promising new developments that await us. Coupled with the exciting advances in developmental neuroscience, propects for the future are never brighter for understanding the developing nervous system from conception throughout childhood.

PEGGY C. FERRY, MI Department of Pediatrics University of Arizona Health Sciences Cente 1501 N Campbell Ave Tucson, AZ 85724

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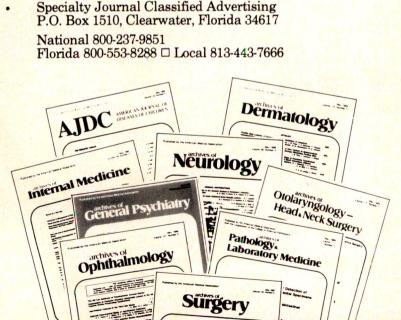
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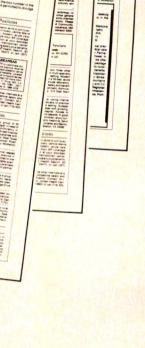
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Special Feature

Radiological Case of the Month

Albert Martijn, MD, PhD; Jan K. M. van Loon, MD (Contributors); Beverly P. Wood, MD (Section Editor)

A 3-year-old girl was brought to the pediatric clinic by her parents, who spoke the language poorly. They said the girl had swallowed something but could not be clear about what the object was. The patient was in good health and the physical examination results were normal. The laboratory findings were normal. Roentgenograms of the digestive tract were obtained. Only the roentgenogram of the abdomen was abnormal (Fig 1).

Accepted for publication March 13, 1989. Contributed from the Departments of Radiology (Dr Martijn) and Pediatrics (Dr van Loon), University Hospital Groningen, Oostersingel 59, 9714 EZ Groningen, the Netherlands.

Reprint requests to the Department of Radiology, Childrens Hospital of Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90027 (Dr Wood).

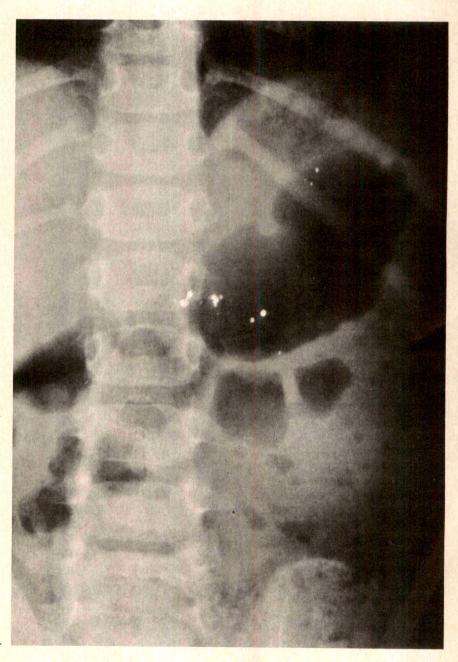


Figure 1.

The Editors welcome contributions to Picture of the Month and Radiological Case of the Month. Those who wish to contribute should send their manuscripts to Dr Feingold (Picture of the Month), National Birth Defects Center, Franciscan Children's Hospital, 30 Warren St, Brighton, MA 02135, or Dr Wood (Radiological Case of the Month), Department of Radiology, Childrens Hospital of Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90027. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.

Denouement and Discussion

Ingestion of Mercury From a Broken Thermometer

Fig 1.—Detail of the anteroposterior roentgenogram of the abdomen, with multiple flecks of mercury in the stomach.

Fig 2.—Detail of the anteroposterior roentgenogram of the abdomen 2 days later, with innumerable tiny mercury droplets in the sigmoid colon and rectum.

The initial roentgenogram shows multiple, small, rounded, opaque globules of heavy metal in the stomach. Elsewhere, the abdomen was unremarkable. After recognition of the ingested material, mercury, it was clear that the child had broken a thermometer and swallowed a piece of it.

Mercury is one of the most recognizable ingested foreign substances. It always has a round shape with a diameter of less than 1 mm to 2 or 3 mm. 1 It is easily distinguished from dental amalgam, which is irregular in shape and sharp in contour and from lead gunshot pellets, which are uniform in diameter. The patient was given oral laxatives and a laxative diet. The roentgenogram 2 days later showed progressive passage of the mercury droplets that had become smaller but remained round (Fig 2). Six weeks after ingestion there was no mercury remaining in the digestive tract. The child was in excellent health and no traces of mercury were detectable in the urine.

Elemental mercury is not toxic when ingested. 1-3 In the gastrointestinal tract it forms drops, and elemental mercury cannot react with biological molecules.3 When lodged in the tissues, it causes local and systemic ill effects.1-2 One has to be sure that all ingested mercury is evacuated from the digestive tract. Inhalation of the highly toxic vapor of mercury can lead to symptoms within several hours. These include weakness, chills, nausea, vomiting, dyspnea, and cough. An interstitial pneumonia can also develop.3 Chronic exposure to mercury vapor leads to acrodynia or "pink disease" in which the neurological effects dominate.3-5

Another foreign body containing mercury is the small dry battery used in cameras and pocket calculators. These are round and of metallic density with a diameter of approximately



Figure 2.

1.5 cm and a thickness of 0.5 cm.^{2.6} These batteries contain mercuric oxide, potassium hydroxide, and zinc. If they open in the gastrointestinal tract, they cause corrosion and ulceration of the mucosa and may lead to elevation of the serum and urine mercury levels with clinical ill effects of mercury intoxication.^{6.7}

Whenever a history of swallowing foreign bodies exists, roentgenography of the entire digestive tract is useful. Knowledge of the roentgenographic appearances of foreign bodies may lead to the correct diagnosis of the ingested material, as in our case, and thus to a proper treatment.

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Special Feature

Picture of the Month

Sami B. Elhassani, MD; Tally Lerman-Sagie, MD; Marc Mimouni, MD; A. Metzker, MD (Contributors);
Murray Feingold, MD (Section Editor)

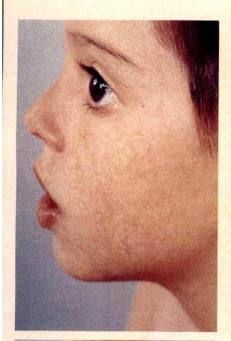




Figure 3.

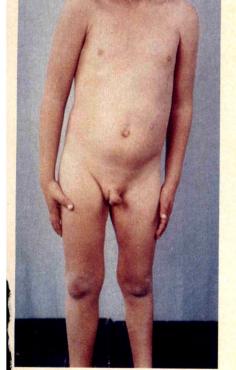


Figure 1.

The statements listed below are best associated with which of the above figures:

Figure 2.

- (a) This condition is not associated with a tumor, and because it is difficult to treat, it may require amputation.
- (b) An asymptomatic upper abdominal mass is present.
- (c) Deep venous abnormalities are associated with this syndrome.
- (d) In this condition, hemiatrophy, and not hemihypertrophy, is present.



Figure 4.

Accepted for publication June 6, 1989. Contributed from the Mary Black Memorial Hospital, Spartanberg, SC (Dr Elhassani), and Beilinson Medical Center, Tel-Aviv, Israel (Drs

Lerman-Sagie, Mimouni, and Metzker).
Reprint requests to the National Birth Defects
Center, Franciscan Children's Hospital, 30 Warren St, Brighton, MA 02135 (Dr Feingold).

Denouement and Discussion

Fig 1.—A reticulated mottled pattern over the face, abdomen, and left leg, with hemiatrophy of the left

Fig 2.—Klippel-Trenaunay syndrome with hemihypertrophy and typical vascular malformation.

Fig 3.—Proximal focal femoral deficiency of the right lower limb.

Fig 4. - Top, Hemihypertrophy of the right lower limb. Bottom, Tongue in patient with Wilms' tumor.

- (a) Proximal femoral focal deficiency (Fig 3) is a congenital defect of unknown cause, usually consisting of a shortening of the proximal portion of the femur, with or without involvement of the pelvic bones. The severity of the condition depends on the presence or absence of the femoral head and the acetabulum. Treatment is directed toward stabilizing the hip. Correction of the leg length discrepancy may require a Syme's amputation above the knee and then fitting with a prosthesis.
- (b) Wilms' tumor, one of the most common renal tumors in children, is associated with a variety of congenital anomalies. Hemihypertrophy occurs in approximately 2% to 3% of all patients with this condition (Fig 4). The hemihypertrophy may not become obvious until the adolescent growth spurt. Two other associated anomalies are genitourinary malformations and aniridia. A deletion of the short arm of chromosome 11 has been reported in families of children with Wilms'

tumor. Other manifestations besides an abdominal mass include abdominal pain or vomiting, hypertension, and gross hematuria. The prognosis is better when the diagnosis is made early.

- (c) Major manifestations of the Klippel-Trenaunay syndrome are a vascular malformation, varicose veins, and hypertrophy of bone and soft tissue (Fig 2). Some physicians believe that arteriovenous fistulas are not part of this syndrome, but part of the Parkes-Weber syndrome. Associated findings include lymphangiomas, syndactyly, polydactyly, oligodactyly, and macrodactyly. The cause of the hemihypertrophy is not definitely known. It has been suggested that it may be due to a local increase in the blood supply to the area; however, the hypertrophy is not always present at the site of the vascular malformation.
- (d) Hemiatrophy is present in cutis marmorata telangiectatic congenita (Fig 1), which includes a persistent cutis marmorata pattern, phlebectasia, spider nevus-like telangiectasia,

atrophic plagues, and areas of ulceration. Hemihypertrophy, and also hemiatrophy, may appear during the first 2 years of life, and its cause is not known.

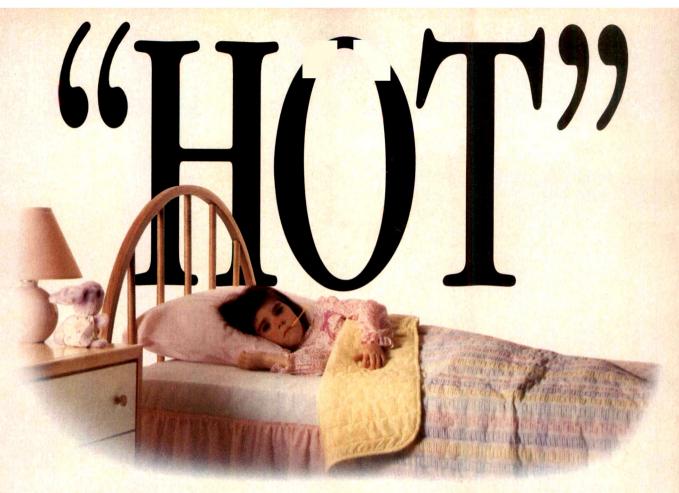
The majority of patients are female and the condition usually occurs sporadically, although there are some reports of autosomal dominant inheritance.

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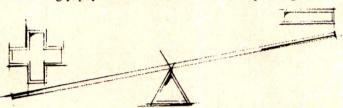
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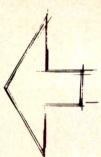


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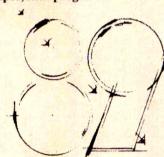


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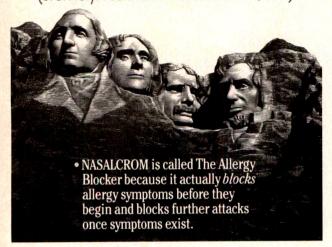
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No evidence of impaired fertility was shown in laboratory animal reproduction studies. Pregnancy: Pregnancy Category B. Reproduction studies with cromolyn sodium administered parenterally to pregnant mice, rats, and rabbits in doses up to 338 times the human clinical doses produced no evidence of fetal malformations. Adverse fetal effects (increased resorptions and decreased fetal weight) were noted only at the very high parenteral doses that produced maternal toxicity. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if

clearly needed. Drug Interaction During Pregnancy: Cromolyn sodium and isoproterenol were studied following subcutaneous injections in pregnant mice. Cromolyn sodium alone in doses of 60 to 540 mg/kg (38 to 338 times the human dose) did not cause significant increases in resorptions or major malformations. Isoproterenol alone at a dose of 2.7 mg/kg (90 times the human dose) increased both resorptions and malformations. The addition of cromolyn sodium (338 times the human dose) to isoproterenol (90 times the human dose)

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While every precaution is taken to ensure accuracy, we cannot guarantee against the possibility of an occasional change or omission in the preparation of this index.

Health and Hospital Readmissions of Very-Low-Birth-Weight and Normal-Birth-Weight Children

William H. Kitchen, MD, FRACP; Geoffrey W. Ford, MB, BS, FRACP; Lex W. Doyle, MD, MSc, FRACP; Anne L. Rickards, MA; Elaine A. Kelly, MA

 Rehospitalizations and health problems at 5 years of age were contrasted between 197 very-low-birthweight (VLBW) children and 47 normalbirth-weight children. At 5 years of age, the VLBW children had a mean of 1.7 hospital admissions and 8.5 days in a hospital: these means were significantly more than the 0.5 admissions and 1.7 days, respectively, for the normal-birth-weight children. Overall, respiratory tract problems and ear, nose, and throat surgery were the most common reasons for readmissions. Malformations and intensive care sequelae infrequently caused readmissions. No combination of sociodemographic or perinatal variables identified the VLBW children who were destined for hospital readmissions. At 5 years of age, the VLBW children, compared with the normal-birth-weight children, had significantly more ongoing sensorineural problems (29.9% and 10.6%, respectively), ongoing respiratory problems (39.6% and 19.1%, respectively), and other morbidities (31.0% and 17.0%, respectively). The VLBW children, compared with the normal-birth-weight children, had more hospital admissions during the first 5 years of life and more ongoing problems at 5 years of age.

(AJDC. 1990;144:2213-218)

Very-low-birth-weight (VLBW) children, ie, those weighing less than 1501 g at birth, have a higher prevalence of later neurodevelopmental sequelae, compared with their normal-birth-weight (NBW) peers. Although there are a number of reports concern-

ing the so-called lesser morbidity and hospital readmissions of VLBW children, they relate mainly to infancy and early childhood, 18 and some relate to a comparison group of NBW children. 2,5,5,8 Reports concerning later childhood ill-

	(n = 197)	(n = 47)	Significance
Grand total, problems	236	25	医生态
Problems per study child mean	1.2	0.5	z=4.04, P=.0001
Grand total, children with ≥1 problems	134 (68.0)	16 (34.0)	$\chi^2 = 17.09, P = .0001$
Sensorineural problems Total No. of children with ≥1 sensorineural impairments	59 (29.9)	5 (10.6)	$\chi^2 = 6.3, P = < .02$
Cerebral palsy	13 (6.6)	1 (2.1)	
WPPSI-FS, <86†	12 (6.1)	1 (2.1)	
Deafness, sensorineural	1 (0.5)	0	
Deafness, conductive	25 (12.7)	3 (6.4)	z=2.58, P<.01
Epilepsy	3 (1.5)	0	
Articulation defect‡	11 (5.6)	1 (2.1)	
Vision, 6/12 or worse OU	7 (3.5)	1 (2.1)	
Respiratory problems Total No. of children with ≥1			
respiratory problem	78 (39.6)	9 (19.1)	$\chi^2 = 6.1, P < .02$
Asthma	35 (17.8)	5 (10.6)	
Recurrent bronchitis	17 (8.6)	1 (2.1)	

29 (14.7)

4 (2.0)

3 (1.5)

61 (31.0)

31 (15.7)

24 (12.2)

13 (6.6)

1 (0.5)

1 (0.5)

3 (1.5)

1 (0.5)

Table 1.—Significant Ongoing Problems at 5 Years of Age*

VLBW

No. (%) of Children

Urinary tract infection

Otitis media

Other problems

Enuresis

Scoliosis

Recurrent tonsillitis

Total No. of children with ≥1

Ventricular septal defect

Recurrent croup

other problem

Psychosomatic§

Deformations

Dermatologic

Accepted for publication July 10, 1989.

Reprints not available.

2 (4.2) 1 (2.1)

8 (17.0)

5 (10.6)

3 (6.4)

1 (2.1)

1 (2.1)

0

0

z = 2.72, P = .007

 $\chi^2 = 3.0, NS$

z = 1.96, P = .05

^{*}VLBW indicates very low birth weight; NBW, normal birth weight; and NS, not significant.

[†]Wechsler Preschool and Primary Scales of Intelligence-full scale, 1 SD or more below the test mean.

[‡]Currently receiving speech therapy.

[§]Encopresis, tics, headache, abdominal pains, and appetite disorder.

^{||}Chest deformity and externally rotated hips.

From the Departments of Obstetrics and Gynaecology (Drs Kitchen and Doyle) and Paediatrics (Dr Kitchen), The University of Melbourne (Australia), and the Royal Women's Hospital, Melbourne, Australia (Drs Kitchen, Ford, and Doyle and Mss Rickards and Kelly).

nesses are sparse and without control populations. 9-11

Data on neurodevelopmental abnormalities, health problems, and hospital readmissions were systematically collected when a cohort of VLBW children was assessed at the ages of 2 and 5 years, and compared with identical information for a group of NBW children. In this report, the ongoing health problems and hospital readmissions for the two groups of children are compared. An attempt is made to identify those VLBW children who are at particular risk of these problems.

PATIENTS AND METHODS

All children in the study were born at the Royal Women's Hospital, Melbourne, Australia; at the time of birth of the study children, approximately 6000 live births occurred annually in this tertiary hospital. There were 85 long-term survivors with a birth weight under 1000 g who were born during the 63 months between January 1, 1977 and March 31, 1982; 83 (98%) were assessed at both 2 and 5 years of age, with the remaining 2 being untraced. These 83 children constituted the extremely-low-birthweight cohort. In addition, there were 123 long-term survivors with a birth weight that ranged from 1000 to 1500 g who were born in the 18 months from October 1, 1980 to March 31, 1982; 114 (93%) were assessed at both 2 and 5 years of age, and they constituted the larger VLBW cohort; and 9 children were either untraced, or the parents refused their child's assessment. The NBW cohort consisted of 60 children (birth weight, >2500 g) who were born contemporaneously with the larger VLBW cohort. This comparison group was selected in a quasi-random fashion by using the terminal digits of the mother's unit record number: data were available at 2 and 5 years of age for 47 (78%) of the children, and the remainder were either untraced or the parents, who had originally consented to participate in the study, subsequently refused the assessment. The children who were not assessed did not differ significantly from those who were assessed for birthweight or the number with fee-paying families or with immigrant mothers. Data on other sociodemographic variables could not be compared because such data were not obtained until the follow-up visit. The project was approved by the Ethics Committee of the Royal Women's Hospital.

The methods used for the assessments for children aged 2 and 5 years has been described7,8; the age of the VLBW children was corrected for prematurity, whether they were small for gestational age or not. The assessment for children aged 5 years included the Wechsler Preschool and Primary Scales of Intelligence, followed by a standard neurodevelopmental examination. Data on ongoing health problems and hospital readmissions (after the primary hospitalization), obtained from the parents at the 2- and 5-year visits, were confirmed, when necessary, by correspondence with relevant hospitals and physicians. Information was coded for each child, first, from the primary hospital discharge until 2 years of age, and, second, from 2 to 5 years of age. For each hospital admission, the duration, diagnosis, and nature of any surgical operations were recorded. At 5 years of age, data on current sensorineural impairments (listed in Table 1)

and ongoing health problems were coded. Asthma was diagnosed if wheezing episodes had been treated with bronchodilators in the previous year.

Biographic data on the children who remained in the three groups of the study to 5 years of age are shown in Table 2. Fee-paying families were those with private medical insurance. Mothers were categorized "immigrants" if they were born in a country where English was not the first language. Social status was assigned according to the occupation of the breadwinner of the family by using the Congalton Scale. 12 Professional and managerial workers constituted classes 1 to 3. skilled and semiskilled workers were in classes 4 and 5, and the remainder, ie, unskilled workers (class 6) and those families receiving social security benefits, were grouped together.

Data were analyzed by a computer with the use of SPSS-X programs. For univariate analyses, differences in proportions were compared by using the χ^2 test, and differences in distribution were compared by using Mann-Whitney U tests as these data were not normally distributed. Multivariate analyses were necessary to adjust for confounding variables. The NBW and VLBW cohorts were compared by a stepwise multiple regression to adjust for the sociodemographic variables (Table 2) and the child's sex on the number and duration of hospital readmissions. For the VLBW cohort alone, we attempted to identify, by multiple regression and discriminant function, a subgroup of children who were more prone to hospital readmissions and risk factors for readmissions, particularly for respiratory problems; the independent variables were sociodemographic (Table 2, older sibling[s] at home), maternal (parity; age, <19 years), and pediatric (gestational age, birth weight, duration of assisted ventilation, duration of supplemental oxygen, bronchopulmonary dysplasia, necrotizing enterocolitis, pneumothorax, and multiple births).

Although the data were analyzed many times, with an increased likelihood of a type I error, many statistical questions were independent, and others were regarded as hypothesis-generating questions, rather than hypothesis-proving questions. Consequently, P values less than .05 were regarded as statistically significant. It also is recognized that type II errors were likely to be high in some analyses that involved only small numbers of subjects with infrequent outcomes.

RESULTS

In the NBW cohort, significantly more mothers were immigrants with a trend toward more fee-paying families, compared with the VLBW children; socioeconomic status and duration of the

Table 2.—Biographic Data on Children in the Study at 5 Years of Age*

	ELBW (n = 83)	Large VLBW (n = 114)	All VLBW (n = 197)	NBW (n = 47)	Significance†	
Birth weight, g Range	540-990	1010-1500	540-1500	2670-6050		
Mean (SD)	863 (98)	1260 (146)	1092 (234)	3560 (71)		
Sex, M	36 (43)	63 (55)	99 (50)	25 (53)		
Immigrant mothers	22 (27)	23 (20)	45 (23)	20 (42)	$\chi^2 = 6.46$ $P = .011$	
Fee-paying family	39 (47)	39 (35)	78 (40)	26 (55)	$\chi^2 = 3.12$ (NS)	
Social status Professional-managerial	11 (13)	25 (22)	36 (18)	13 (28)		
Skilled, semiskilled	46 (56)	47 (41)	93 (47)	13 (28)	z =2 (NS)	
Unskilled, social security	26 (31)	42 (37)	68 (35)	21 (44)		
Maternal education, <10 y	29 (35)	39 (34)	68 (35)	20 (42)	z =3 (NS)	

^{*}ELBW indicates extremely low birth weight; VLBW, very low birth weight; NBW, normal birth weight; and NS, not significant.

[†]Comparison of all VLBW and NBW children.

Table 3.—Surgical (Operative) and Medical (Nonoperative) Readmissions of VLBW and NBW Children to 5 Years of Age*

		Readmissions per Study Child)	% (No.) of Children Readmitte	
	VLBW (n = 197)	NBW (n = 47)	VLBW (n = 197)	NBW (n = 47)
All admissions Total No. of admissions	331 (1.7)	25 (0.5)†		
Total No. of children with ≥1 admissions		25 (0.5)	65.0 (128)	42.6 (20)†
Total No. of surgical admissions	131 (0.66)	22 (0.23)†		
No. of children with ≥1 operation			39.6 (78)	21.3 (10)‡
Ear, nose, and/or throat	49 (0.25)	2 (0.04)	19.3	4.2‡
Ocular	10	0	5.1	0
Malformations	14	1	5.1	4.2
Trauma	3	3	1.5	6.4
Inguinal hernia Girls	2	0	2.0 (2/98)	0 (0/22)
Boys	21)	0)	20.2 (20/99)	0 (0/25)‡
Orchidopexy	9	0	4.1	0
Hydrocele	1 (0.34)	0 (0.08)‡	0.5	0
Circumcision	3	2	1.5	4.2
Intensive care sequelae	10	0	3.6	0
Other	9	3	5.6	8.5
No. of children with ≥1 nonoperative admission		4	39.6 (78)	23.4 (11)
otal No. of medical				
admissions	206 (1.05)	14 (0.3)†		
Asthma	33 (0.17)	5 (0.11)	7.6	10.6
Infections Respiratory tract	81]	3]	1]
Gastroenteritis	28	2		
Febrile convulsions	10 (0.64)	0 (0.17)‡	37.1	12.8‡
Pertussis	2 (0.04)	(0.17)4	37.1	12.01
Pyrexial, cause unknown	5	0		
Meningitis/encephalitis	1)	3		
Trauma, burns, and poisons	11	1	5.6	2.1
Caretaking problems	10	0	4.1	0
Other	25	0	9.6	0

^{*}VLBW indicates very low birth weight; NBW, normal birth weight.

mother's schooling were comparable between groups (Table 2).

There were no significant differences between the extremely-lowbirth-weight and larger VLBW children for the number of hospital readmissions, the number of days of readmission, or the number of ongoing health problems. Consequently, for all further analyses, the extremely-low-birthweight and larger VLBW cohorts were combined to form the group of 197 VLBW children.

Hospital Readmissions

Up to 5 years of age, the VLBW children averaged approximately three times the number of hospital readmissions, compared with the NBW children (1.7 and 0.5, respectively; z=3.96; P = .0001) (Table 3). This difference was also significant when nonoperative and operative readmissions were compared separately (mean nonoperative admissions, 1.0 and 0.3, respectively; z = 2.46; P = .016) (mean operative admissions,

0.7 and 0.2, respectively; z=2.66; P = .008) (Fig 1).

The VLBW children had approximately five times the mean number of days in the hospital, compared with the NBW cohort (respective means, 8.5 and 1.7; z = 3.92; P = .0001) (Fig 2). These differences were also significant if admissions for children aged 2 years or younger and for children aged older than 2 years to 5 years or younger were compared separately (respective means: ≤2 years of age, 6.0 and 1.3; z = 2.25; P = .02; and respective means: >2 and ≤ 5 years of age, 2.5 and 0.4; z = 3.13; P = .002) (Fig 2).

For the VLBW children up to the age of 2 years, medical (nonoperative) readmissions predominated over surgical (operative) readmissions (72% and 18%, respectively), but between 2 and 5 years of age, the proportions were similar (46% and 54%, respectively, Fig 1).

Overall, 65% of the VLBW children were readmitted at least once by 5 years of age, compared with only 43% of the NBW children (Table 3: relative risk $[RR] = 1.5, \chi^2 = 7.1, P < .01$). By 5 years of age, 40% of the VLBW children were readmitted for one or more surgical operations, almost twice the rate of 21% of the NBW children (Table 3: RR = 1.9. $\chi^2 = 4.8$, P < .05); 40% of the VLBW cohort were readmitted for medical reasons, compared with 23% of the NBW cohort (Table 3, RR = 1.7, χ^2 = 3.6, not significant).

The predominant reasons for surgical readmission of VLBW children were for diseases of the ear, nose, and throat (49 [37%] of 131 operations), followed by inguinal hernia (23 [18%] of 131 operations) (Table 3). The 99 VLBW boys had more operations than the 98 VLBW girls, largely because 34% (34/99) of the former had genitourinary surgery (for an inguinal hernia, an undescended testis, a hydrocele, or an elective circumcision). The VLBW boys required significantly more genitourinary surgery than NBW boys (Table 3).

Ten VLBW children required surgery for congenital malformations; the important ones were 1 case each of syndactyly, Meckel's diverticulum, gastroesophageal reflux associated with repaired esophageal atresia, gastroesophageal reflux requiring fundoplication, Fallot's tetralogy, and a renal mal-

[†]P<.01.

[‡]P<.05.

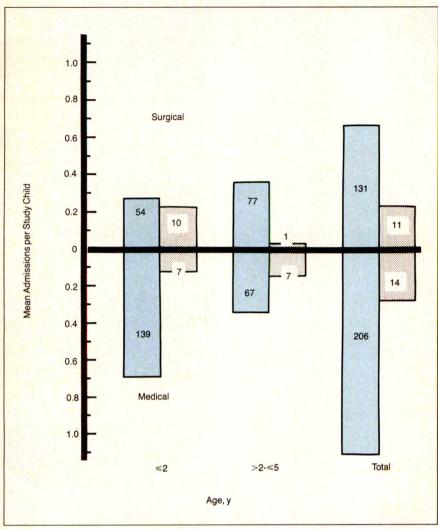


Fig 1.—Comparison of mean number of individual readmissions of very-low-birth-weight children (open bars) and normal-birth-weight children (shaded bars) for surgical and medical indications. Numbers in bars indicate number of children.

formation requiring three operations; the 4 other malformations were trivial (Table 3).

Only 10 operations on seven children were sequelae of neonatal intensive care (Table 3)—4 bronchoscopies in two children with subglottic stenosis and 1 operation each of nasal stenosis, closure of an ileostomy, retinal cryotherapy, removal of a Rickham's reservoir, and gangrene of a hand (2 operations).

The medical indications for readmissions are listed in Table 3. The VLBW children were significantly more often readmitted to the hospital with infections or pyrexia (Table 3). Respiratory tract infections were the predominant cause for readmission, with significantly more readmissions in the VLBW chil-

dren (z=2.50, P=.01); respiratory infections constituted bronchitis, bronchiolitis, croup, pneumonia, otitis media, and tonsillitis. Readmissions for asthma were not significantly more prevalent in the VLBW cohort (Table 3).

Ongoing Health Problems

Ongoing problems at 5 years of age occurred significantly more frequently in the VLBW children, compared with the NBW children (an average of 1.2 and 0.5 problems per child, respectively; 68% of the VLBW children had one or more ongoing problems at 5 years of age, ie, twice as many as the 34% of children in the NBW cohort (RR = 2.0) (Table 1). Significant differences per-

sisted in both the numbers of individual problems and the number of children with problems if the latter were subdivided into three categories of sensorineural, respiratory, and other problems (Table 1). Respiratory tract problems were the most frequent cause of ongoing morbidity in the VLBW children (40%), ie, more than twice the rate in the NBW children (19%) (RR = 2.1). Sensorineural problems, although less frequent than respiratory tract problems, were almost three times more frequent in the VLBW children (30%) than in the NBW children (11%) (RR = 2.8) (Table 1). At 5 years of age, sensorineural impairments (Table 1) were causing a significant functional disability in 38 (19.3%) of the VLBW children and in 2 (4.3%) of the NBW children ($\chi^2 = 5.2$, P = .02). The disability was severe in 9 (4.6%) of the VLBW cohort and in 2 (4.2%) of the NBW cohort (cerebral palsy with severe motor disability and/or Wechsler Preschool and Primary Scales of Intelligence-full scale under 70); 29 (14.7%) of the VLBW children and none of the NBW children had a mild to moderate functional disability (children with one only of the following impairments-Wechsler Preschool and Primary Scales of Intelligence-full scale, 70 to 85; cerebral palsy with mild to moderate physical impairment; deafness requiring hearing aids; epilepsy; and visual acuity, ≤6/36 OU). Sensorineural impairments in the remaining 21 VLBW children were causing little or no functional disability.

Multivariate Analyses

In comparing the NBW children with the VLBW children, the increasing number of hospital admissions (the dependent variable) was associated with the VLBW category (5.1% of variance, P = .0001) and male sex (additional variance, 3.9%; P = .002), non-feepaying status (additional variance, 2.1%; P = .02), and children of nonimmigrants (additional variance, 2.4%; P = .01). The increasing number of days of hospital readmission was associated with the VLBW category (3.2% of variance, P = .0006), non-fee-paying status (additional variance, 3.2%; P = .0004), and nonimmigrant status (additional variance, 1.9%; P = .03).

In the VLBW cohort alone, sociode-

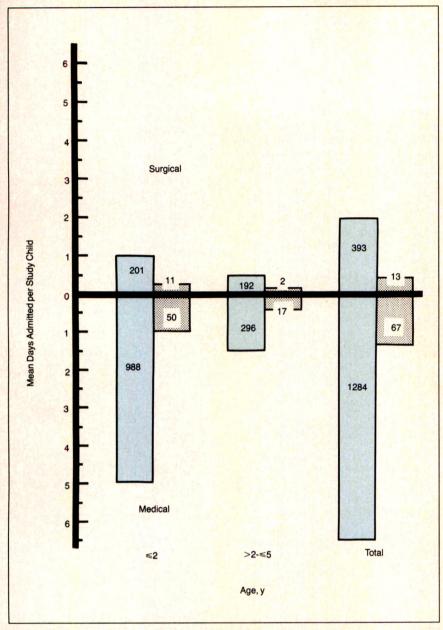


Fig 2.—Comparison of mean number of days of readmissions of very-low-birth-weight children (open bars) and normal-birth-weight children (shaded bars) for surgical and medical indications. Numbers in bars indicate number of children.

mograhic and medical data available during the primary hospitalization were unhelpful in identifying those children who were destined for hospital readmissions. In a discriminant function analysis with hospital readmission as the dichotomous dependent variable, significant independent variables predicted 89% (114/128) of the children who were readmitted, but it incorrectly predicted the readmissions of 73% (50/69) of those children who were not readmitted. Attempts to predict nonoperative

and operative readmissions separately were equally unhelpful. The discriminant function analyses could not accurately predict readmissions in the samples from which they were derived; they could only be worse at predicting readmissions if applied to separate samples of children.

In the VLBW cohort, with the increasing total number of readmissions as the continuous dependent variable in a stepwise multiple regression analysis, 15.8% of variance was accounted for by

five significant independent variables: male sex, 5.2% (P = .001); nonimmigrant status, 3.2% (P = .01); older sibling(s) at home, 3.1% (P = .01); maternal age younger than 19 years, 2.6% (P=.02); and noninsured families, 1.8% (P=.05). In a second regression analysis with the total days of readmissions as the dependent variable, only 9.8% of variance was accounted for by three significant variables: uninsured families, 3.7% (P=.007); older sibling(s) at home, 2.7% (P=.01); and nonimmigrant status, 3.4% (P = .01). Regression analyses with operative and nonoperative admissions as dependent variables provided no additional useful infortion.

In the VLBW cohort, variables associated with an increasing number and duration of readmissions for respiratory tract problems were next explored. With total admissions for respiratory tract problems as the continuous dependent variable, 5.0% of variance was accounted for by two significant variables: older sibling(s), 2.9% (P=.03); and male sex, 2.1% (P=.04). For increasing duration of respiratory readmissions, male sex accounted for 2.5% of variance (P=.03).

COMMENT

Our study indicates that VLBW children, compared with NBW children, continue to have significantly more readmissions between 2 and 5 years of age; other studies in this age range also report many readmissions but lack a comparison group to confirm that the rate is excessive. 10,11 The preponderance of medical readmissions in the first 2 years of life confirms the findings from other reports.1-5 From 2 to 5 years of age, the rates of surgical and medical readmissions were similar largely because medical admissions were reduced. Ear, nose, and throat operations and respiratory tract infections were the most frequent single surgical and medical reasons for readmission, respectively. The VLBW children had neither significantly more readmissions for asthma nor ongoing asthma at 5 years of age.

We were unable to identify a group of VLBW children who were destined for readmissions from data available at the conclusion of their primary hospitalization. Three sociodemographic vari-

ables-nonimmigrant status of the mother, families without private health insurance, and older sibling(s)-although statistically associated with more readmissions, were of limited clinical value. Boys were more often readmitted, only partly because of the large proportion who had inguinal and genital surgery. We were surprised to find in the VLBW children that the decreasing birth weight and gestational age and the increasing duration of ventilation and oxygen dependency were not statistically significant precursors of either total hospital readmissions or all admissions associated with the respiratory tract. McCormick et al² were likewise unable to predict readmissions in the first year of life, although Combs-Orme et al13 and Glass et al14 were more successful. Because cohorts of VLBW children are widely divergent sociodemographically and techniques of intensive care change so rapidly, predictions from individual studies are likely to be of parochial rather than generalized utility. This is disappointing for it prevents vigorous intervention in a small, at-risk population, aimed at reducing the need for hospitalization.

Despite the frequent readmissions of VLBW children, they consitute only about 1% of the child population, so that the impact on overall usage of hospital resources is small. The influence of rehospitalization on the future development of the child, in contrast to an early report, They may be less important as the needs of the young child in a hospital are

met more adequately. 16 Nevertheless, any illness in a young child, especially if hospitalization is involved, may be disruptive to the family unit.

Ongoing problems at 5 years of age predominated in the VLBW children, although not all would be regarded as serious. However, the list in Table 1 is incomplete: notable omissions are poor growth, 17 behavior disorders, and minor visual morbidity, which has been reported previously. 7,8,10 Furthermore, educational difficulties are anticipated, 11,18-20 although the children in our study are too young to assess their prevalence. As an indication of professional resource utilization, this report is incomplete, for it does not quantitate hospital clinic visits and medical consultations or the use of intervention programs other than speech therapy.

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The Use of Hygiene, Cohorting, and Antimicrobial Therapy to Control an Outbreak of Shigellosis

Richard E. Hoffman, MD, MPH, Pamela J. Shillam

 Shigellae are easily transmitted in day-care centers to children and adult staff by contamination of diaper-changing surfaces and fomites or directly from person to person. Appropriate antimicrobial therapy may shorten the duration of diarrhea caused by shigellae and eliminate the organism from the feces. Current recommendations of the American Academy of Pediatrics and the American Public Health Association are that infected children be isolated until three and two, respectively, consecutive stool cultures are negative. We utilized a disease control strategy based on use of antibiotics to control diarrheal symptoms and reduce infectiousness, cohorting of asymptomatic infected children in the center, and scrupulous attention to hygiene and environmental cleanliness. This strategy was effective in stopping transmission, was more practical than some of the measures now recommended by the American Academy of Pediatrics and the American Public Health Association, and was well accepted by parents and center staff. The strategy should be evaluated in other day-care settings.

(AJDC. 1990;144:219-221)

Shigellae have frequently been reported to cause outbreaks of acute infectious diarrhea in day-care centers. 13 This has been attributed to the low inoculum necessary to produce disease and the ease with which shigellae can be identified in the laboratory. Like other enteropathogens spread in the day-care center environment, shigellae are easily transmitted from the index case to other children and day-care center personnel by contamination of diaper-changing surfaces and fomites or directly from person to person.

A variety of infection-control strategies have been used to control diarrhea

in day-care centers: handwashing, ⁵ environmental cleaning, ^{6,7} physical separation of ill from well children, ¹³ exclusion of ill children, ⁸ cohorting ill children, ¹ closing the center, ³ and temporary exclusion of new admissions to a center. ¹⁻⁸

Both the American Academy of Pediatrics (AAP) Committee on Infectious Diseases9 and the American Public Health Association (APHA)10 recommend antibiotic treatment of cases of shigellosis in day-care centers and isolation of infected persons until three and two, respectively, stool cultures taken 24 hours apart (after cessation of antimicrobial therapy) are negative. While the AAP Committee on Infectious Diseases recognized that appropriate antimicrobial therapy may shorten the duration of diarrhea and eliminate the organism from feces, the recommendations for control of shigellosis in day-care centers do not distinguish the untreated child with diarrhea from the asymptomatic carrier.

Strict adherence to the AAP and APHA recommendations requires that the infected child be isolated for many days: antimicrobial treatment is usually given for 5 days11; 24 to 48 hours after cessation, the first culture is taken and repeated daily for 2 more days, and often 2 more days elapse waiting for culture results. If the child is excluded from the day-care center until proved noninfectious, there is considerable inconvenience and/or expense for working parents. Most parents are willing to miss work to care for the child when he or she is acutely ill; however, when the child is asymptomatic and recuperating, the parent usually must find alternative child care. The child may be taken to a day-care home or another day-care center, potentially exposing more children. As noted by Pickering et al,4 "for fear of being absent from their jobs, parents of the children often conceal illness, and sick children continue to attend the centers."

In this report, we describe an out-

break of shigellosis that occurred in a Denver, Colo, child-care center in 1987. We tried new control methods because of problems encountered by one of us (R.E.H.) in controlling a similar child-care center outbreak in Albuquerque, NM, in 1979 using measures recommended by the AAP and APHA.

DESCRIPTION OF THE OUTBREAK

On September 24, 1987, the director of a Denver child-care center called the state health department to report that an adult staff member had been hospitalized with diarrhea and dehydration, and a stool culture was positive for Shigella sonnei. The organism was sensitive to ampicillin and trimethoprim and sulfamethoxazole. The director reported that in the previous 2 weeks, 16 of 24 children in a classroom for children of ages 30 to 47 months had become ill with an acute diarrheal illness. During the same 2-week period, 5 cases of acute diarrheal illness had also been reported in three other classrooms.

There were 126 children and 24 employees regularly attending the center: two classrooms for children aged 18 to 29 months, one classroom for children aged 30 to 47 months, and three classrooms for children aged 4 to 6 years. An investigation of usual hygienic practices at the center found that restrooms were mopped twice a day; toys were usually cleaned once per week; in the younger children's classrooms, diapers were changed by any available staff person; nondiapered children were instructed to wash their hands before and after meals and after using the toilet but often went to the toilet unsupervised; meals and snacks were served "family style"; children of all ages were grouped together before and after regular center hours (8 AM to 5 PM) and on the playground; and children regularly used common play dough, corn meal, and water games.

As shown in the Figure, 38 persons (31 children and 7 adult staff) met the case definition of either a positive stool culture for *S sonnei* or fever and diarrhea (two or more loose stools per day). The overall attack rate was 25%; 37 of the 38 cases were symptomatic. Twenty-five cases had positive cultures (3 adults and 22 children), and 24 of these were symptomatic. All rectal swabs were performed by either parents or center staff. All positive cultures were

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confirmed as *S sonnei* in the Colorado Department of Health, Denver, bacteriology laboratory.

Attack rates by age group are presented in the Table. Children aged 30 to 47 months had the highest rate (96%), followed by adult staff (29%). The children aged 30 to 47 months were in one classroom; 23 of 24 children and 5 of 5 adult staff in this classroom developed illness and had positive cultures, indicating infection in virtually all susceptible persons in this classroom. The 7 adult cases came from three classrooms, and the 31 child cases came from five classrooms.

The Figure shows that by the time the first case was reported to public health officials, 21 cases (55% of the total number of cases) had occurred. The time from first report of the outbreak until the onset of the last case was 8 days. Forty-five percent (n=17) of the cases occurred after the first report. Infection-control measures were initiated on September 25, although they were not fully implemented for several days. Theoretically, there were 128 susceptible persons when the outbreak was first reported.

CONTROL MEASURES Children and Staff With Diarrhea

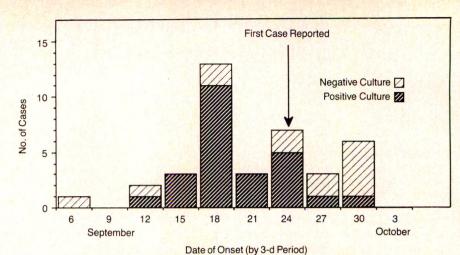
Children and staff with diarrhea had cultures performed and were excluded from the center until they had received appropriate antimicrobial therapy for 72 hours and had no symptoms; they could then return to their regular classroom at the center while completing their course of therapy. If the person did not take antibiotics, he or she could not return to the center until he or she was asymptomatic and had two consecutive negative stool cultures at least 24 hours apart.

Previously Symptomatic Children

Children who had diarrhea in the previous 3 weeks and were asymptomatic as of September 24 were presumed to have had shigellosis and to be infectious. They were required to undergo antimicrobial therapy to remain in the center and were cohorted in a "sick" room until completion of 72 hours of treatment, after which they could then return to their regular room.

Culture Surveys

All children and staff in two classrooms—the one containing children



Epidemic curve for shigellosis outbreak at a Denver, Colo, child-care center in 1987.

Age Group	Cases With Onset Prior to First Report	Total No. of Cases	No. of Positive Cultures	No. of Persons in Age Group	Overall Attack Rate, %
18-29 mo	1	5	2	30	17
30-47 mo	16	23	18	24	96
4-6 y	2	3	2	72	4
Adult staff	2	7	3	24	29

aged 30 to 47 months and the classroom for children 18 to 29 months in which one ill child had been described—were required to have stool cultures. Staff were given instructions on how to collect a stool culture (rectal swab or fecal material in the diaper, underwear, or toilet tissue), and thereafter all cultures were obtained by staff and/or parents. Any person who developed diarrheal symptoms while in attendance at the center immediately had a culture performed and was excluded.

Asymptomatic, Culture-Positive Children

Asymptomatic, culture-positive children were cohorted in a "get well" room until they completed 72 hours of antimicrobial therapy.

Increased Hygiene

The following measures were instated to increase hygiene: (1) toys were placed in a bin after each use; they were cleaned with a disinfectant (1/4 cup of bleach to 1 gal of water) before other children were allowed to play with them; (2) food was served individually; (3) restrooms were cleaned hourly; (4) diapers were changed twice per half day

and as needed by only one person who had no other responsibilities in a classroom; (5) children's hands were washed several times per half day under supervision by adult staff; (6) the center directors reemphasized for adult staff the need to wash one's hands after changing diapers, after toileting, and before feeding children; (7) use of corn meal, play dough, and water games was suspended; and (8) combined classrooms before and after regular center hours were suspended.

New Admissions

New admissions to the center were not permitted until 2 weeks after the onset of diarrhea of the last child with *S sonnei*.

Community Notification

The following steps were taken to notify the community of the outbreak: (1) all licensed child-care centers in Denver were notified of the outbreak and instructed to exclude any child with diarrhea or history of exclusion from another center; (2) all pediatricians, family practitioners, and emergency department physicians were mailed a bulletin describing the outbreak, public health

control measures, and sensitivity patterns of the epidemic organism; and (3) meetings were conducted with parents at the center to explain infection-control policies, and parents were instructed not to take excluded children to other child-care facilities.

Center Policy

Parents were not charged for days when their child was excluded.

Surveillance

Active surveillance for diarrheal illness and culturing of symptomatic persons was maintained for 3 weeks after the onset of illness in the last reported case.

COMMENT

The objectives of the infection-control measures taken by public health officials in the 1987 Denver shigellosis outbreak were to prevent new cases of diarrhea from occurring, to keep the day-care center open and operational, and to prevent spread of shigellae to other child-care centers.

We believe these control measures are more practical than the current AAP and APHA recommendations. Antimicrobial therapy was used to stop symptoms and reduce infectiousness; we then permitted children and staff to return to the center where careful hygiene and environmental controls were used to control transmission. This was similar to the strategy used by Tauxe et al in center A during a shigellosis outbreak in Seattle, Wash, in 1983. Meticulous hygienic technique is necessary to interrupt transmission of Shigella. A study by Ekanem et al6 documented widespread environmental contamination in day-care centers during outbreaks of diarrhea caused by enteric bacteria; they found an increase (relative to nonoutbreak periods) in the percentage of positive cultures for fecal coliforms on the classroom floor, toys, table tops, kitchen counters, tap handles, flush handles, and diaper-changing areas.

Performing a rectal swab is no more invasive than taking a rectal temperature, which parents and center staff are accustomed to doing. Utilizing families and staff to culture persons with diarrhea may increase the speed of detection of new infections and enhance surveillance. Rectal swabs may also be

taken by trained public health nurses; however, we have observed that in most child-care centers there is not a time in the day when all attendees are present.

The disadvantage of having public health nurses perform culture surveys at appointed times is that some children may be missed. The children who do not undergo cultures usually remain in the center, potentially leading to mixing of infected and uninfected children. On the other hand, there is a valid concern that parents and staff may exercise poor technique, resulting in false-negative cultures; we instructed parents and staff to make sure the end of the swab had visible brown fecal material on it. We have observed symptomatic children who had negative cultures in a physician's office and positive cultures by

Excluding children while they are ill with diarrhea and permitting them to return to the center when they are asymptomatic makes sense to working parents who cannot afford time off waiting for culture results. Parents, therefore, may be less likely to take an infectious child to another center. From the center's viewpoint, enrollment levels may not be lowered for as long a time. Thus, the policy enhances cooperation of both the center staff and parents with public health officials during the stress of an outbreak of diarrhea.

Pediatricians, family practitioners, and other primary health care providers have an important role in the control of day-care center shigellosis. The disease is self-limited and frequently mild. In isolated cases, there may be little reason to treat a patient. The AAP Committee on Infectious Diseases, therefore, states that "the primary indication for treatment in some patients is to prevent further spread of the organism." For this reason, we provided information about the outbreak and treatment recommendations to health care providers.

This report does not scientifically demonstrate the efficacy of the infection-control procedures used in the 1987 Denver outbreak. We verified that excluded children remained at home and took their antimicrobial medications by talking with parents and attending physicians, as well as by checking attendance records at the center. No outbreaks of shigellosis were reported at any other child-care center in metropol-

itan Denver in either September or October 1987.

When compared with previously published reports, 1,2 the Denver outbreak was controlled relatively rapidly-8 days from first report to onset of illness in the last case. We believe this was due to the infection-control measures rather than exhaustion of susceptible persons. because only 14% (21/150) of the center staff and attendees had developed illness by the time the policies were implemented. The staff's conscientious attention to hygiene at all levels of activity in the center was essential in helping control the outbreak. We recognize that such extensive changes in day-care center operation may not be possible in every center experiencing a shigellosis outbreak. In a subsequent outbreak at another center in Denver, slightly less stringent measures were used due to physical constraints and staffing limitations; nevertheless, the outbreak was controlled rapidly using the same protocols for treatment, exclusion, and culturing. Therefore, the Denver approach should be evaluated in other settings.

Michael Burkkart, MPH, Donna Chitwood, John Humphreys, Ray Jansen, Alan Nansel, John Pape, Marilyn Shahan, RN, and Rachel Wood, MD, provided assistance in outbreak control and review of the manuscript.

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Determinants of Milk Flow Through Nipple Units

Role of Hole Size and Nipple Thickness

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• The aim of the present study was to elucidate the role of hole size and thickness in determining milk flow through nipple units during bottle feeding. Commonly used standard nipple units (SMA singlehole, Enfamil single-hole, and Twist-on) for term and preterm infants, as well as Nuk-type nipple units (SMA Nuk, Enfamil Natural, and Nuk) were tested. The size of the nipple hole and wall thickness were determined for each nipple unit. Airflow was measured by forcing pressurized air through the feed hole. Simulated sucks were used to measure the milk flow. A marked variability in airflow and milk flow was observed within and among the various types of nipple units studied. Within each type of nipple unit, both milk flow and airflow measurements correlated well with hole size. The thickness of the nipple units contributed minimally to the observed variability. We conclude that differences in hole size primarily account for the observed variability in milk flow. This finding may be clinically important in that rapid milk flow can lead to apnea and bradycardia in some preterm infants. The above observations imply that design changes are necessary to reduce the variability of milk flow within each nipple type. Moreover, milk-flow measurements made using a simple mechanical system and airflow measurements used by the industry are equally sensitive to evaluate nipple

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A number of different types of nipple units are available for use in neonates; some are specially designed for premature infants, whereas others are designed to resemble the human nipple. At present, most preterm infants are

fed with nipple units designed for preterm infants. However, the functional superiority of these types of nipples over other types for these infants has not been adequately documented. For instance, the assumption has been made that preterm infants generate less pressure per suck and the preterm nipple units are therefore designed to deliver higher flow compared with nipple units designed for term infants. However, it is not clear whether there is any advantage in increasing the milk flow in preterm infants. On the contrary, higher milk flow may produce some adverse effects by altering the breathing pattern significantly.

The milk flow through nipple units can be altered by a number of factors: the characteristics of the nipple, the rigidity of the container, and the sucking pressure generated by the infant.1-8 Since the pressure generated by the infant varies from suck to suck and from infant to infant, we have developed a system with which we can evaluate the different nipple units at a constant sucking frequency and pressure. Since rigid containers are used, the differences in milk flow can be attributed solely to differences in nipple characteristics. Recently, we reported a marked variability in milk flow within the same type and among the different types of nipple units. We speculated that the size of the nipple hole is the most important variable in determining milk flow; the thickness of the nipple unit may also contribute to variability.

The aim of the present study was to establish the role of these two variables in determining milk flow. An additional objective of the study was to compare the milk-flow determinations of the simple mechanical system with airflow measurements, the industry standard.

MATERIALS AND METHODS

Nipple units commonly used in the feeding of newborn infants formed the basis of this study. These nipple units were manufactured and/or distributed by Mead-Johnson (Evansville, Ind), Ross Laboratories (Columbus, Ohio), and Wyeth (Philadelphia, Pa), and consisted of standard nipple units for term and preterm infants as well as the Nuk-type units. The general characteristics of these nipple units have been reported previously.¹

The following tests and measurements were conducted on each nipple: the size of the nipple hole, the thickness at the tip of the nipple, the airflow, and the milk flow. The size of the nipple hole was calculated using a profile projector (Mitutoyo Manufacturing Co). The diameter of the hole was measured along the x and y axes. The average of the two values obtained was taken as the diameter of the feed hole. The wall thickness was determined using a Magna-Mike thickness gauge (Automatic Inspection Device, Inc). The wall thickness was measured by using a small steel ball on the inside of the nipple and a magnetic probe on the outside of the nipple's bulb. The gauge senses the magnetic field strength between the ball and the tip of the probe. Since the magnetic field varies in a known manner with the distance between the ball and probe, the wall thickness can be calculated accurately with a microprocessor. The airflow was measured by inserting the nipple into an orifice and then inserting a plunger into the nipple forcing pressurized air (42 psi) through the feed hole. The flow rate of the air passing through the nipple was measured with an airflow meter.

The milk flow through the nipple was measured as reported previously.¹ Briefly, the nipple to be tested was firmly secured on a bottle containing ready-to-feed formula (Enfamil, 281 kJ/dL), inverted, and placed on a rigid container. A negative pressure pulse of –120 cm H₂O at 40 cycles per minute was then applied to the rigid container with a breast pump. The number of sucks required to empty a bottle with 120 mL of formula was determined and was inversely proportional

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to milk flow. Twenty nipple units were evaluated in each category.

Stepwise linear regression analysis was used to correlate the hole size and wall thickness to airflow and milk flow rates. A value of P < .05 was considered significant.

RESULTS Nipple Units for Term Infants

The results obtained with various nipple units are summarized in the Table. In general, Nuk-type nipples had larger feed holes compared with standard nipple units for term infants. Among the nipple units for term infants, the largest percentage variation in hole size was observed with the Twist-on nipple unit for term infants, made by Ross Laboratories. Among the standard types, the greatest thickness at the tip was observed with the Twist-on nipple unit, and among the Nuk types, the greatest thickness was observed with the SMA unit. The SMA singlehole unit had the largest percentage variation in thickness among the standard units, and the Enfamil Natural had the largest percentage variation in thickness among the Nuk-type nipple units (Table).

Greater hole size was associated with higher airflow and milk flow (indicated by a smaller number of simulated sucks). Regression analysis revealed a highly significant (P<.001) correlation between hole size and airflow as well as between hole size and milk flow for standard nipple units (Fig 1). This correlation was not significantly improved by the addition of thickness. As for the standard nipple unit, a highly significant (P<.005) correlation existed between hole size and airflow as well as between hole size and milk flow for SMA Nuk units and Enfamil Natural units. whereas the correlation was less significant (P < .05) for the Nuk nipple distributed through Ross Laboratories (Fig 2). Thickness significantly improved this correlation with milk flow only with the SMA Nuk nipple unit.

Nipple Units for Preterm Infants

These nipple units had larger feed holes compared with their counterparts for term infants for Enfamil and smaller feed holes for SMA nipple units (Table). Both airflow and milk flow were correspondingly higher with Enfamil and lower with SMA units for premature

Comparison of Various Types of Nipple Units Used in the Neonatal Period

	Mean±SD							
Nipple Units	Hole Size, cm	Thickness,	Airflow, mL/s	Milk Flow*				
	Те	erm Infants	hills her					
Standard								
SMA single-hole	0.043 ± 0.003	0.077 ± 0.012	30.7 ± 2.8	777 ± 106				
Enfamil single-hole	0.036 ± 0.004	0.084 ± 0.011	24.4±3.6	1068 ± 185				
Twist-on	0.031 ± 0.008	0.127 ± 0.015	5.1 ± 2.7	627 ± 268				
Nuk-type								
SMA	0.069 ± 0.004	0.132±0.015	52.1 ± 3.5	135±11				
Enfamil Natural	0.040 ± 0.003	0.116±0.020	25.9 ± 3.3	342±56				
Nuk	0.055 ± 0.004	0.110±0.012	42.3±3.5	183 ± 49				
	Pret	term Infants						
Standard								
SMA single-hole	0.039 ± 0.005	0.131 ± 0.015	23.8 ± 5.3	827 ± 180				
Enfamil single-hole	0.054 ± 0.005	0.115±0.016	43.1 ± 2.9	320 ± 37				
Twist-on	0.032 ± 0.007	0.111 ± 0.022	28.8 ± 10.3	705 ± 480				

^{*}Values represent the number of simulated sucks to empty a bottle with 120 mL of formula.

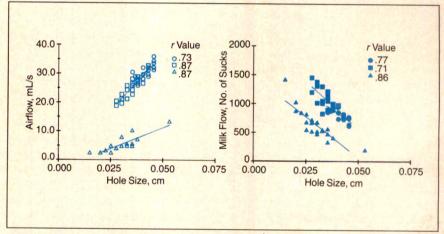


Fig 1.—Standard nipple unit for term infants. The circle indicates SMA single-hole unit; the square, Enfamil single-hole unit; and the triangle, Twist-on unit. Open symbols indicate airflow; solid symbols, milk flow. The higher the number of sucks, the lower the milk flow.

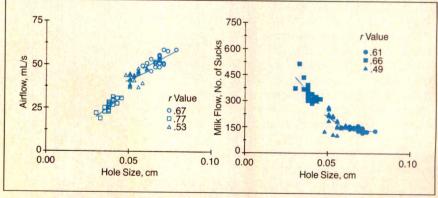


Fig 2. — Nuk-type nipple units. Correlations between airflow and hole size and milk flow and hole size are shown. Triangles indicate the Nuk nipple distributed through Ross Laboratory. See Fig 1 for definitions of other symbols.

infants. Again, regression analysis showed highly significant (P<.001) correlations between hole size and airflow as well as between hole size and milk flow (Fig 3). No significant correlation between thickness and airflow or milk flow was observed with any of the nipple units.

COMMENT

Using simulated sucks, we recently reported a great variability in milk flow within and among the various types of nipple units available for use in newborns.1 Results of the present study confirm and extend this observation. The number of simulated sucks fell within the 2 SDs reported previously.1 The marked variability observed in both studies underscores the variability in milk flow seen with these nipple units. As a result of the earlier study, we hypothesized that differences in the size of the nipple hole probably accounted for most of the observed variability in milk flow and we suggested that rapid milk flow may lead to apnea and bradycardia in some preterm infants.1 The present results clearly document that milk flow and airflow correlate well with the size of the nipple hole. This correlation was observed with all the different types of nipple units studied. The difference in thickness (within the ranges studied) did not significantly improve the correlation between hole size and milk flow, except with the SMA Nuk nipple.

Our results indicate that airflow and simulated sucks are both equally good in evaluating functional characteristics of the nipple (Figs 1 through 3). However, simulated sucks employ relatively simple methods compared with the airflow measurements used by the industry. Moreover, since simulated suck evaluates milk flow rather than airflow, and since it employs negative pressure pulse rather than constant positive pressure, this form of evaluation resembles more closely the physiological conditions observed during bottle feeding.

We did not measure directly the distensibility of the nipple units. Instead, we chose to measure the wall thickness at the tip of the nipple, which is an indirect measure of distensibility. For most

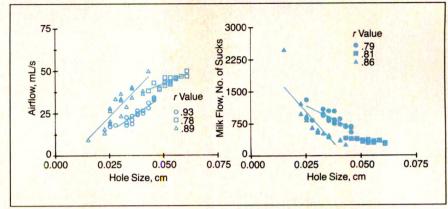


Fig 3. —Standard nipple units for preterm infants. See Fig 1 for definitions of symbols.

of the nipple units studied, there was a poor correlation between nipple thickness and airflow or milk flow. Hence, wall thickness at the tip, at least in the ranges studied, does not appear to be an important determinant of milk flow.

Even though it is clear that differences in hole size are primarily responsible for the variation in milk flow, the various tests used did not reveal the reason for this variability. One likely explanation is the methods used in making the feed hole. The feed holes are drilled mechanically, a method that would be expected to produce significant variation in hole size. Innovations in this technique, such as the use of laser, may help reduce this variation in hole size. Preliminary data on laser-cut nipple units indeed support this contention (O.P.M., unpublished data, 1989).

A decrease in ventilation during nipple feeding is well documented in both term and preterm infants. 4,5 Among preterm infants, the reduction in ventilation is greater in the more premature groups.5 Even apnea and bradycardia may occur in some of these infants.6 Immaturity of the central nervous system presumably is responsible for the above observation. Alternatively, the high milk flow present in these studies may have contributed, at least in part, to the adverse effects mentioned above. If this assumption is true, the occurrence of apnea and bradycardia can be reduced significantly by decreasing the milk

Our results raise several questions. Do we need nipple units specially designed for premature infants? If so, how should these differ from nipple units designed for term infants? How much variability in flow characteristics is acceptable among nipple units designed for a specific group of infants, such as term or preterm infants?

The present study documents that the wide variability in flow characteristics of the nipple units is due primarily to differences in the size of feed holes and suggests the need for design changes to reduce the observed variability.

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Hypothalamic Hamartomas and Sexual Precocity

Evaluation of Treatment Options

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 We describe four male patients with hypothalamic hamartomas associated with sexual precocity. Our assessment of their management suggests that resection using current microsurgical techniques is a valid treatment option if the patient has a normal pubertal endocrine makeup, if the hamartoma is pedunculated, and if the patient is young enough to require years of parenteral medical treatment. Such surgical treatment can be curative, and subsequent growth and development can be normal (patients 1 and 2). However, if the patient is near to pubertal age (patient 3) or if neurosurgical or gonadotropin releasing hormone analogue treatment is not available, the natural history (patient 4) suggests that the only undesirable effects are accelerated growth, tall stature for age, and premature sexual development during childhood, as well as the psychosocial problems that may accompany them. Adult height may be compromised, although the two patients who did not undergo a surgical procedure and did not receive gonadotropin releasing hormone analogue therapy are above the lower limits of the normal range of adult male height. Therefore, if the hamartoma is pedunculated and cessation of pubertal development is desired, resection of the hamartoma is a reasonable therapeutic option.

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The association of hypothalamic hamartomas and sexual precocity is well known, although the relationship of cause to effect has not been clearly es-

tablished. Traditionally, as long as a patient was neurologically normal and early puberty was the only finding, no treatment was given except perhaps medical therapy to attempt to suppress pubertal development. Recently, gonadotropin releasing hormone (Gn-RH) analogue therapy has been demonstrated to suppress pubertal development in these patients. Treatment with Gn-RH analogue should be considered in these patients.

In addition, because of the advent of more accurate diagnostic techniques and better microsurgical techniques, surgical treatment of these patients needs to be reconsidered. Not only are more patients with sexual precocity that is related to hamartomas likely to be identified with the better visualization techniques of computed tomography (CT) and magnetic resonance imaging (MRI), but neurosurgical intervention now has a low morbidity, and therefore some hamartomas can be totally removed without neurologic sequelae.

We report herein the history of four boys with sexual precocity and hypothalamic hamartomas and discuss their different treatments and the indications for neurosurgical intervention.

PATIENTS AND METHODS

The medical records of four patients who had presented with sexual precocity and hypothalamic hamartomas were reviewed. Three patients were able to be contacted and seen for clinical assessment.

Hormonal assessment included plasma measurements of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone values of 8.8, 7.3%, and 8.6% for mean values of 8.8, 23.6, and 34.6 IU/L for 20 consecutive assays, respectively. For FSH, the interassay coefficient of variation

was 6.8%, 4.7%, and 5.1%, respectively, for 20 consecutive assays with mean values of 6.7, 13.2, and 32.0 IU/L. The interassay coefficient of variation for testosterone was 5.7% and 8.2% for 20 consecutive assays of quality control samples with means of 13.03 and 1.32 nmol/L.

REPORT OF PATIENTS

PATIENT 1.—When this boy was 9 months of age, his parents noted the development of an enlarged penis, as reported previously.⁵ When examined at 13 months of age, his height was at the 90th percentile, he had a muscular build, his penis was 10.5 cm long, and he had pubic hair at Tanner stage 2. Laboratory data are given in the Table.

An initial CT scan was interpreted as normal. However, a repeated scan, 3 months later, showed a questionable suprasellar mass. Cisternography demonstrated a 5- to 6-mm pedunculated mass attached to the floor of the third ventricle. A right-sided temporal craniotomy was performed. A pedunculated mass attached to the tuber cinereum was removed. Postoperatively, his testosterone, LH, and FSH levels decreased to the prepubertal range. Secondary sex characteristics regressed and growth decelerated. Growth and development have been normal postsurgically for the past 7 years.

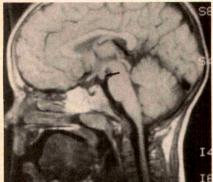
PATIENT 2.—According to the parents, this patient had appeared muscular and had a large penis since birth. At 19 months of age, his voice was deep, and the skin on his forehead and back was oily. At 23 months, pubic hair began to develop, and his pediatrician verified the enlarged penis and noted somewhat enlarged testes. Data are given in the Table.

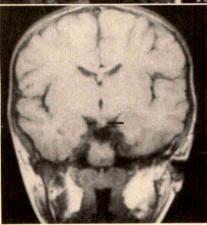
When examined at Children's Hospital of Pittsburgh (Pa), the patient appeared muscular and older than his chronologic age, and his height and weight exceeded the 90th percentile. Growth rate was documented to be excessive over the previous 6 months. He had punctate papules over the skin of his forehead and shoulders. His penis was broad and measured 6.5 cm in length. His right testis was 3×2 cm and his left was 2.5×2 cm.

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Sagittal (top) and coronal (bottom) T₁-weighted magnetic resonance images demonstrating the sessile mass (arrow) below the hypothalmus, in the suprasellar cistern.

The skin over the scrotum was thin with rugae. His pubic hair was at Tanner stage 2.

Testosterone and gonadotropin levels before and after Gn-RH stimulation showed a pattern consistent with puberty. Blood samples for LH and FSH were drawn every 20 minutes from 10 PM to 2 AM and showed a pattern consistent with pulsatile release. His bone age was 4 years. A CT scan of the head showed a 7×7-mm mass below the tuber cinereum, posterior to the infundibulum. The sella and ventricles were normal. An MRI study demonstrated a rounded mass about 6 mm in size inferior and anterior to the mamillary bodies consistent with a hamartoma (Figure). The patient was given Gn-RH analogue (480 µg of leuprolide acetate [Lupron] subcutaneously, daily; 30 µg/kg per day), and 1 month later the testosterone level indicated partial suppression (Table). A decision was made to attempt to excise the hamartoma surgically and the injections were stopped. When he was 27 months of age, a right temporal craniotomy was performed. The hamartoma was just anterior to the basilar artery and was adherent to the inferior surface of the hypothalamus. The tumor was dissected off the hypothalamus, transecting the broad-based stalk. A $6 \times 5 \times 3$ -mm mass was excised. Postoperatively, a transient partial right-sided oculomotor palsy was

The tumor was composed of a disorganized mass of neurons, astrocytes, and scattered

blood vessels, consistent with a hamartoma. Electron microscopy showed scattered astrocytes with neurons embedded in a matrix of astrocytic processes. Neural processes with dense-core granules were also noted.

Six months postoperatively, the patient showed regression of testicular size, thickening of scrotal skin, and complete loss of his pubic hair. His testosterone and gonadotropin levels had decreased to prepubertal levels. Eighteen months later he still had no evidence of resumption of pubertal physiology.

PATIENT 3. - At 8 years 7 months of age, this boy was noted by his parents to have deepening of the voice, development of body odor, and body hair. His height and weight had always been at or just above the 95th percentile. His growth rate had recently accelerated so that both height and weight were at 3.5 SDs above the mean for age. Neurologically, the child had always been normal, and there was no history of meningitis or encephalitis. At 8 years 11 months of age, he was a healthy boy who appeared somewhat older than his stated age. The right testis was 4.5 cm in its long axis and the left was 5 cm. Stretched penile length was 12 cm and pubic hair was at Tanner stage 3. The remainder of his physical examination results were normal for age.

His testosterone and gonadotropin levels were pubertal (Table). Gonadotropin responses to Gn-RH were also pubertal. Bone

Hormonal Data*							
			LI	LH, IU/L		FSH, IU/L	
Patient No.	Treatment	Age, y	Basal	Peak-Gn=RH	Basal	Peak-Gn = RH	Testosterone nmol/L
1	No treatment	1.17	15.4		1.9		13.00
	Postresection	1.92	<1.3		2.0		0.35
2	No treatment	2.05	10.4		8.3		12.45
		2.10	6.3	61.9	4.6	10.0	30.10
		2.15					18.72
	Leuprolide acetate, 2 wk	2.20	8.9	and the same of	3.0		8.25
	No treatment	2.30	4.6		2.8		22.68
	Surgery	2.31	2.1		1.5		
		2.33	<1.3		<0.8		2.39
		2.55	<1.3		<0.8		0.35
3	No treatment	8.9	<1.3	65.6	<0.8	13.1	18.97
		9.6	10.9		2.9		25.62
		10.2	2.3		4.3		15.88
4	Danazol	4.5	5.5				14.46
		5.9	13.8		6.5		
		7.5	8.6		10.8		
Normal pre	epubertal		<1.3-5.8	≈22	<0.8-5.20	≈7.6	< 0.35
Normal pul		61	>1.3-12.4	≈50	<0.8-10.5	≈8.4	>0.70

^{*}LH indicates luteinizing hormone; FSH, follicle-stimulating hormone; and Gn-RH, gonadotropin releasing hormone.

age was 12 years 9 months. A CT scan of the head showed a 1-cm soft-tissue mass in the suprasellar cistern. The mass did not enhance after administration of a contrast medium. An MRI scan confirmed the CT finding. Because of the near-pubertal age of the patient and his projected height of 175 to 178 cm, with his father being 177 cm tall, the patient was not treated. At age 11 years he had full pubertal development and was 164 cm tall. Final height has not yet been achieved.

PATIENT 4.—In 1971, at age 4 years 6 months, this boy presented to Johns Hopkins Hospital, Baltimore, Md, for evaluation of accelerated growth. Sexual precocity dated back to age 2 years, when his mother noted the development of pubic hair, enlargement of the penis, and rapid increase in height. Neurologically, he had been normal.

At examination his height was 129 cm (>95th percentile) and his weight was 28.1 kg (>95th percentile). He was a muscular child with Tanner stage III pubic hair, an adult-sized penis, rugated scrotal skin, and testes measuring 4 × 2.5 cm on the right and 3.5×2 cm on the left. Results of neurologic and ophthalmologic examinations were normal. Testosterone and gonadotropin levels were in the adult range (Table), 24-hour urinary ketosteroid levels were 2.6 mg, and the bone age was 11 years. Pneumoencephalography disclosed a 2-cm mass in the interpeduncular cistern without an apparent point of attachment. At age 4 years 6 months, he was given danazol. Over the next 3 years his genitalia were unchanged and his bone age advanced to 14 years 6 months. Pneumoencephalography was repeated and showed that the size of the mass had not changed. By 8 years 9 months of age, his growth had decelerated considerably, and danazol therapy was discontinued. At 10 years of age, his height was 163.4 cm, and his bone age was 18 years, gonadotropin and testosterone levels being in the adult range. He was last seen at 20 years of age, was doing well, and was neurologically normal. His height was 165 cm (at the 3 to 5 percentile for adult males). Computed tomographic scans done in the interim disclosed that the tumor size had not changed.

COMMENT

Precocious puberty in boys is defined as the onset of puberty before 9 years 6 months of age. True precocious puberty implies normal hormonal stimulation with capacity to reproduce. It is also referred to as central precocious puberty because it is initiated through activation of the hypothalamic-pituitary-gonadal axis. The cause of true precocious puberty is unknown for most patients.

Among known causes are tumors, trauma, irradiation, and inflammatory diseases.

Of the tumors that cause precocious puberty, the hypothalamic hamartoma is the most common and is being diagnosed more frequently. While the association between hypothalamic hamartomas and sexual precocity has been recognized for a long time, new and refined therapeutic interventions are now possible and should be considered. Before 1980, 37 cases of hypothalamic hamartomas associated with precocious puberty were reported. Since 1980, an additional 54 patients have been described. The likely reason for this increase is the use of CT and MRI.

Precocious puberty caused by hamartomas tends to occur earlier in life than that due to other causes.12 The clinical findings include the development of pubic hair and genital maturation. Often the boys appear more muscular than one would expect for their age. Growth is accelerated and bone age is advanced. Deepening of the voice and the appearance of acne are common. Other clinical findings that may be associated with sexual precocity and hamartomas include mental retardation, behavioral disturbances, gelastic seizures, absence seizures, or, occasionally, generalized seizures. Such findings were present in 48% of the patients in the review of Zuniga et al.

Gonadotropin levels may be in the adult range, and response to Gn-RH stimulation is exaggerated for age. Nocturnal studies of gonadotropin secretion show pulsatile release. Testosterone levels are pubertal. It is usually assumed that there is early maturation of mechanisms that control Gn-RH release either by directly secreting Gn-RH in a pulsatile secretory pattern or by blocking usual prepubertal inhibitory influences.

Pneumoencephalography was used previously to detect hypothalamic hamartomas, but this technique is now obsolete since the advent of enhanced imaging (CT, MRI). The use of MRI to detect and describe such hamartomas is optimal. Sagittal, coronal, and axial views that enable better visualization of the tumor can be obtained with MRI.²⁴

Not all tumors that are visualized in the hypothalamic area of children with sexual precocity are hamartomas. If tumors do not have the exophytic configuration typical of hamartomas, a biopsy is recommended to determine if the mass is a glioma and anaplastic. Low-grade gliomas are usually treated by radiotherapy and high-grade gliomas by both radiotherapy and chemotherapy. However, the treatment for hamartomas is less well defined.

Treatment of sexual precocity associated with hamartomas, as with central sexual precocity in general, should be generalized. In both situations, there is the option not to treat. Reasons for treatment are to allow growth and pubertal development to occur at an ageappropriate time. This may avoid considerable psychosocial stress and prevent premature skeletal maturation and a shorter adult stature. The facts of each patient need to be examined to weigh the advantages of treatment vs no treatment. In the patients with hamartomas, the nontreatment option exists because there is no evidence that the tumors associated with sexual precocity and no neurologic abnormalities will grow or subsequently cause other problems.

The reason to treat, then, is if it is believed to be appropriate to stop the progression of puberty and premature skeletal maturity. Such treatment would have been better for patient 4, who lived his entire childhood with the awkwardness of being fully developed sexually. Even though his height reached the lower limit of the adult normal ranges, he was tall and cumbersome throughout childhood and as an adult is substantially shorter than familial expectations. On the other hand, intervention may not be indicated if pubertal development becomes evident only slightly early, as in patient 3, if adjustment to the early pubertal development is satisfactory, or if expected adult height is not seriously compromised.

The best medical treatment is with long-acting Gn-RH analogues. This treatment is effective among patients with hamartomas and will stop pubertal maturation and slow the rate of skeletal maturity. This therapy is effective in reducing basal levels of LH, FSH, and testosterone. Most secondary sexual characteristics do not progress and may regress. The rates of growth and bone

age advancement decrease. While this mode of therapy is an option for all forms of central precocity, the longrange effects are not yet known. However, such treatment is expensive and requires regular administration of medication until an age appropriate for pubertal development. The decision made in patients 1 and 2 for surgery was in part because the Gn-RH analogue would have to be administered for almost a decade. The cost, the prolonged parenteral administration, and the unknown effects of such long-term treatment were all factors that led to the decision for surgery in these instances.

The option for surgical removal of hypothalamic hamartomas that are pedunculated needs to be reconsidered. The previous conclusion that the associated surgical risks make it a poor treatment option⁶ does not necessarily apply in light of refined techniques. While a re-

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view of the literature since 1958 reveals generally a poor outcome among the 33 cases in which hamartomas that caused precocious puberty were treated surgically. 5,6,11-18,20-23,25-34 subtotal resection or biopsy only was done in the majority of cases. Outcome was reported for 22 of 27 with subtotal resection. Arrested puberty or clinical regression was reported in 7, regression of hormonal levels in 7, and both in 1. Among 6, persistence of puberty or no regression was seen, and in 1 death occurred owing to operative complications. Surgical treatment then should not be attempted unless total resection would appear to be possible. However, among 6 with total resection, only 3 had arrested puberty, and in 1 the tumor initially regressed but subsequently recurred. However, in 4 of the previously reported cases, including our patient 1,5 the tumor was clearly pedunculated. 6,14,20 We can now add pa-

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cocious puberty and hypothalamic hamartoma: report on a new case with ultrastructural data. *Acta Neurochir*. 1985;74:129-133.

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tient 2 and state that in all 5 cases puberty regressed although it recurred in 1.² This is the basis for our position that neurosurgical removal may be a treatment option when pedunculated hamartomas are visualized, making complete resection probable without unjustified risk of neurologic damage.

With MRI scans, the morphologic nature of hypothalamic hamartomas can be clearly determined. ²⁴ Because pedunculated and sessile masses can be excised with low morbidity and the precocious puberty possibly cured using current microneurosurgical techniques, when very young children present with sexual precocity and tumors of the right configuration, resection should be considered as a treatment option. Conversely, surgery to obtain biopsy specimens is not indicated and will not modify the precocious puberty.

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New Insights Into Idiopathic Infantile Arterial Calcinosis

Three Patient Reports

Sandra Juul, MD; Daniel Ledbetter, MD; Thomas N. Wight, PhD; David Woodrum, MD

 We describe the occurrence of idiopathic infantile arterial calcinosis in three newborn siblings. Unusual features in this disease include ultrasonographic prenatal diagnosis in the second two siblings and ultrastructural studies of the third patient that might shed light on the pathophysiologic characteristics of this disease. Ruthenium-red staining for proteoglycans showed a clearly abnormal structure for the granules in areas of calcification. The granules appeared disorganized, with loss of their normal honeycomb interconnections. They also varied in size and density. In addition, matrix vesicles that might serve as nucleation sites for crystalline calcium phosphate were observed in zones of calcification.

(AJDC, 1990;144;229-233)

I diopathic infantile arterial calcinosis (IIAC) is a rare condition characterized by medial calcification and intimal proliferation of large and medium-sized arteries throughout the body. In affected infants, feeding intolerance, respiratory distress, hypertension, or signs of heart failure usually occur in the first month of life. Laboratory findings include normal serum calcium, phosphate, and electrolyte levels. Once symptomatic, the patient usually suffers from progressive, unremitting heart failure, which is fatal.

The cause of this disease remains unknown, although previous reports have speculated that it results from an abnormality of elastin fibers, 1.8 altered iron metabolism, 4 altered ion and fluid exchange between mother and fetus, 5 or that it is a response to intimal hyperplasia. 6

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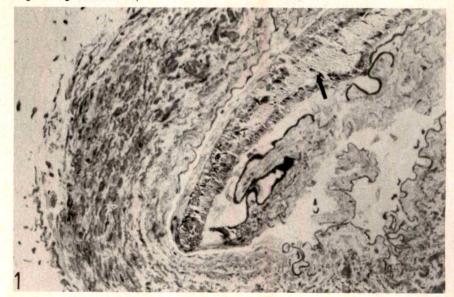
We describe a family with three affected children. There was no consanguinity in the parents, and no other members in the extended family were affected. This family is unique, as the diagnosis was made prenatally by ultrasound examination in two of the infants. Some insight about the time of onset of calcification and the ability to make the diagnosis prenatally can be gained. This family also helps to clarify the genetic transmission of this disease. In addition, ultrastructural studies using the hexavalent dye ruthenium red to stain negatively charged molecules, such as proteoglycans (PGs), suggest the involvement of PGs in the calcification process.

METHODS

Segments of aorta were fixed in halfstrength Karnovsky's solution buffered at a pH of 7.4 in 0.1 mol/L of sodium cacodylate in the presence of 0.2% ruthenium red for 3 hours at room temperature.7 Primary fixation was followed by several rinses in 0.1 mol/L of sodium cacodylate buffer containing 7.5% sucrose and 0.1% ruthenium red, and the specimens were then left overnight in this buffer at 4°C. The segments were postfixed in 1% osmium tetroxide containing 0.05% ruthenium red for 3 hours at room temperature, dehydrated in graded alcohols, and embedded in epoxy resin. Thick sections were cut with glass knives and stained with Richardson's stain. Thin sections were cut with diamond knives, stained with uranyl acetate-lead citrate, and examined in an electron microscope at 60 kV. These studies were performed on patient 3 only.

Collagen analysis was performed on cultured fibroblasts from patients 2 and 3 using described methods. Briefly, cells are labeled with 3.7×10 bq/mL of tritium-labeled proline in the presence of ascorbic acid for 16 hours, after which they are processed on a

Fig 1.—Light micrograph of a portion of calcified aorta from patient 3 with idiopathic infantile arterial calcinosis. Arrow indicates area of intense intimal calcification (Richardson's stain, original magnification × 16).



Reprints not available.

5% acrylamide gel for screening purposes, checking the size and amounts of bands.

PATIENT REPORTS

PATIENT 1.-A 2180-g male infant was born at 32 weeks' gestation to a healthy 24year-old woman, who was gravida 2, para 2, with one living healthy child. The mother developed hydramnios at 30 weeks' gestation. Serial fetal ultrasound examinations were performed, and by 32 weeks, the fetus showed progressive edema and poor myocardial contractility. A cesarean section was performed for progressive idiopathic nonimmune hydrops. Apgar scores at 1 and 5 minutes were 3 and 5, respectively. The patient was intubated, and treatment for heart failure was begun. Systolic blood pressure was elevated, ranging from 120 to 170 mm Hg, but diastolic pressure remained in the normal range. The plasma renin level was 30 times the upper limit of normal. The hypertension was not responsive to hydralazine hydrochloride but was controlled with captopril. A renal ultrasound examination was performed in search of an explanation for the infant's hematuria and decreased renal function (creatinine reading of 160 µmol/L), and it unexpectedly led to the diagnosis of IIAC, as echogenicity of the aorta and its branches was noted.9 The patient died at 1 month of age with intractable heart failure.

Autopsy revealed extensive medial calcification and intimal hyperplasia of the aorta and its branches including the coronary arteries. Calcification between myocardial fibers and microscopic calcification within the renal tubules and glomeruli were present. Cystic infarcts of the putamen and caudate nucleus were also present, apparently the result of hypoxic damage.

PATIENT 2.—The second patient was conceived 1½ years later. A prenatal ultrasound at 18 weeks' gestation was normal. At 31 weeks' gestation, hydramnios developed. By 32 weeks, progressive hydrops with poor cardiac contractility was apparent. A computed tomographic scan prior to delivery showed aortic and renal artery calcification. The male infant, delivered by cesarean section, was grossly edematous and moribund. Apgar scores at 1 and 5 minutes were 1 and 1, respectively, and the patient died at 34 minutes of life.

At autopsy, extensive patchy calcification of the internal elastic lamina and media of the aortic, coronary, pulmonary, renal, mesenteric, splenic, and peripheral arteries was confirmed. The mineralized deposits caused disruption of the normal pattern of elastic fibers. The subclavian and abdominal arteries demonstrated extensive intimal hyperplasia with greater than 50% luminal occlusion. Calcification of arteries was evident in the putamen, and foci of coagulative necrosis



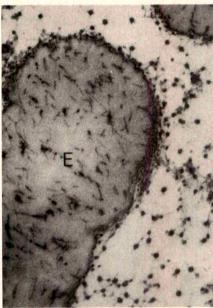


Fig 2.—Top, Electron micrograph of a portion of extracellular matrix from a noncalcified zone from the aorta of patient 3. Numerous ruthenium red–positive granules identifying proteoglycans (arrow) are dispersed throughout the extracellular matrix interconnected by thin filamentous threads. Collagen fibrils (C) and components of the elastic fiber (E) are also prominent. Bottom, Electron micrograph of an area adjacent to that shown above demonstrating numerous ruthenium red–positive granules adjacent to and in close association with an elastic fiber (E) (original magnification × 38 564 [top], × 35 974 [bottom]).

were seen within the head of the caudate nucleus and internal capsule. Calcification here was less regular but more dense than in other vessels and involved the entire thickness of the vessels. The pituitary gland contained spherical calcific concretions. Biochemical analysis of collagen types yielded normal findings.

PATIENT 3.—The third patient was conceived 1 year later. Multiple prenatal ultrasound examinations were normal until 31 weeks' gestation when calcification of the fe-

tal aorta and upper iliac vessels was noted. Progressive hydrops followed, and spontaneous labor began at 33 weeks' gestation. A moderately hydropic female infant was delivered by cesarean section. Echocardiogram on day 1 of life showed calcification of all great vessels, coronary arteries, ductus arteriosus, and endocardium. Moderate pericardial fluid was present. Hypertension was a significant problem, with systolic pressures in the range of 140 to 180 mm Hg and diastolic pressures between 35 to 90 mm Hg.

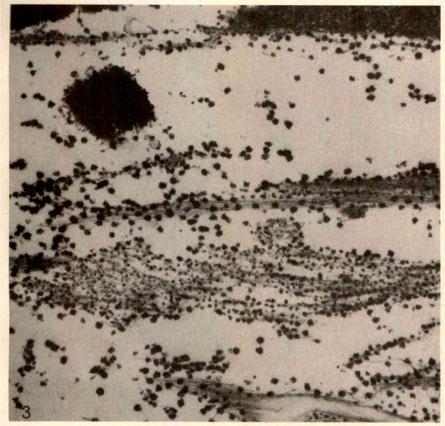


Fig 3. —Electron micrograph from a portion of the calcified zone in the aorta of patient 3. Calcified clefts are prominent in the upper left portion of the micrograph. Ruthenium red-positive granules are enlarged as their aggregation is disrupted when compared with those shown in Fig 2 (original magnification × 39 493).

After unsuccessful trials of captopril, hydralazine, and furosemide (Lasix), hypertension was well controlled with nifedipine (0.5 mg administered sublingually). Renal function was poor as reflected by a serum urea nitrogen level of 14.5 mmol/L and a creatinine reading of 280 µmol/L. On day 19 of life, she became hypotensive and bradycardic and died.

Autopsy showed diffuse medial and intimal calcification of aortic, coronary, pulmonary, celiac, renal, and peripheral arteries. Cardiomegaly (heart weight, 29 g and normal weight, 14.5 g) with soft-tissue calcinosis in some areas of the myocardium and papillary muscles was present. No evidence of infarcts was noted. Spherical calcifications involving the glomerular tufts and parietal portion of Bowman's capsule were noted, as well as calcific concretions within renal tubules. Calcification of arterial walls of globus pallidus and sublenticular regions was present, as was focal necrosis and calcinosis of the head of caudate nucleus and internal capsule. Results of biochemical analysis of collagen types were normal. Ultrastructural studies revealed marked abnormalities in arterial PGs.

RESULTS

Light microscopy revealed extensive calcification within the intimal portion of the aorta (Fig 1). Ultrastructural examination of this area demonstrated portions of the intima that were heavily calcified while other areas exhibited no signs of calcification. In noncalcified areas, the matrix consisted of numerous ruthenium red-positive granules interconnected via fine filamentous threads forming a honeycomb network (Fig 2). These interstitial granules were uniform in size and stellate in shape with smooth contours. The granules were associated with the microfibrillar and elastin component of the elastin fiber (Fig 2). Smaller ruthenium red-positive granules were associated with collagen fibrils at regular intervals (Fig 2, top).

In calcified areas, this organization was markedly altered. Near bands of calcific deposition, the ruthenium red-positive granules were disorganized and no longer arranged in a well-spread

honeycomb pattern (Fig 3). Instead, the organization of the granules was disturbed, and the granules occurred in clumps with little or no evidence of interconnection (Fig 3). In addition, the granules in the calcified zone were significantly larger, had indistinct contours, and were more electron dense. These larger granules were particularly prominent near areas where crystalline structures appeared and at times seemed to merge with the dense-staining calcific plaques (Fig 3). These large amorphous granules appeared attached to both components of the elastic fiber in a random, dispersed fashion (Fig 3). In agreement with other studies,4 some of the elastic fibers contained electrondense material and appeared heavily calcified (Fig 4), while cross sections of collagen fibrils revealed electron densities resembling calcium spicules associated with the outer edges of some of the collagen fibrils. Some areas of the calcified zones showed electron-dense vesicles, delineated by a membrane and clearly associated with the dense ruthenium red-positive granules (Fig 5). These structures resembled matrix vesicles described in other calcifying systems. 10

COMMENT

Typically, patients with IIAC present early in infancy with nonspecific complaints such as vomiting, feeding intolerance, diarrhea, tachypnea, hypertension, 6,11,12 cyanosis, or heart failure. In addition, several cases of fetal-bydrops have been reported, with IIAC diagnosed at autopsy. 18,14 Once a patient has become symptomatic, an unremitting course to death has followed with few exceptions. 9,16

Refractory hypertension has been a major problem in several patients who have been described. Poor compliance of major vessels and increased renin levels secondary to decreased renal blood flow with renal artery involvement have been implicated. Focal calcifications in the glomeruli have also been reported. Hypertension was an important clinical aspect in two of these newborns. The hypertension in patient 1 was well controlled with captopril (an angiotensin-converting enzyme inhibitor). The hypertension in patient 3 was unresponsive to this drug but exquisite-

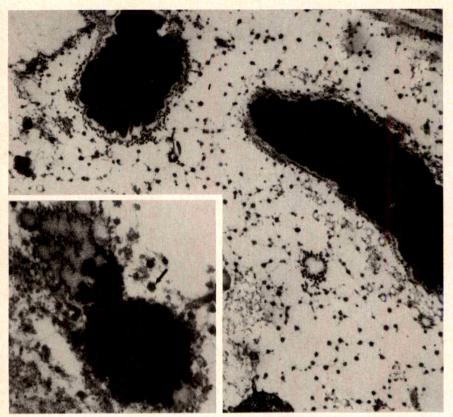


Fig 4.—Electron micrograph of calcified zone demonstrating extensive calcification of the elastic fibers from patient 3. Inset, Higher magnification demonstrates partial calcification of an elastic fiber. Amorphous enlarged ruthenium red—positive granules (arrow) lie adjacent to the calcifying zone (original magnification × 38 917, × 68 888 [inset]).

ly sensitive to nifedipine, a calcium channel blocker. In previous patient reports, nifedipine has not been mentioned. Congestive heart failure and myocardial ischemia are the most commen causes of death, due to coronary artery occlusion. 6 This was the putative cause of death in all three of our patients. Vessels in the brain have been relatively spared, although two reports mention cerebral vessel involvement,6 and one survivor is reported to be mildly mentally retarded. 17 Two of the children in this family had calcification of the basal ganglia and are therefore unusual. To our knowledge, the pituitary involvement present in patient 2 has never been described before.

Recurrence in siblings has been reported^{4,17}; however, the exact mode of transmission has been unclear. In this family, the genetic pattern of inheritance is clarified somewhat, as two affected children were male and one was female, thus eliminating an X-chromosome–linked mode of transmission. Al-

ternatively, an autosomal dominant pattern with mosaicism in one parent or variable penetrance⁴ is possible, although unlikely, as their family history is otherwise normal. An autosomal recessive mode of transmission is most likely.

Even with the diagnosis of IIAC in mind, prospective prenatal ultrasound examinations of two affected infants in this family appeared normal until the third trimester, when calcifications were noted and the simultaneous onset of hydrops began. This limits the usefulness of ultrasonography in prenatal diagnosis. Further research is needed to determine a genetic or biochemical marker, allowing a more effective prenatal diagnosis to be made.

Idiopathic infantile arterial calcinosis is an example of "calcific disease." These diseases are characterized by early calcium deposition, tissue dysfunction secondary to this calcium deposition, and evidence that control of calcification could lead to decreased

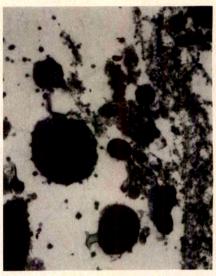


Fig 5. — Electron micrograph from a calcified zone of patient 3 reveals a number of membrane-bound vesicles surrounded by ruthenium red—positive granules (original magnification × 43 660).

morbidity and improved prognosis of the disease. Although the process of calcification has been studied at length, it remains unclear which factors are actually involved and in what sequence. A significant literature exists suggesting that matrix vesicles that are membrane-delimited particles enriched in phospholipid and phosphatase enzymes serve as the site of initial extracellular calcification. 4 Alternatively, others suggest that extracellular matrix components, such as PGs, promote calcification since these molecules are enriched in regions where calcification occurs. 19 For example, a number of studies using elemental analysis have demonstrated the codistribution of sulfur (a prominent component of PGs) and calcium in calcifying tissue. 20,21 In 1978, Morton, 2 using light microscopic histochemical techniques, observed intense staining for PGs in zones of calcification in blood vessels from three fetal patients afflicted with IIAC. Other studies have demonstrated coincident staining of PGs and calcium in blood vessels as well.22 Furthermore, the hypothesis implicating PGs in calcification predicts that for calcification to occur where high concentrations of PGs exist, a redistribution in the structural organization of these matrix molecules must occur. 19 Studies of calcifying cartilage have shown a decrease in the degree of PG aggregation and a cleavage of hyaluronic acid, which forms the backbone of the PG aggregate during calcification. ^{19,23-25} Interestingly, the intact PG aggregate inhibits calcification in vitro, ^{28,27} suggesting that the degree of PG aggregation may be one of the factors that influences the calcification process.

The results of the present study suggest an involvement of PGs in IIAC. First, the normal architecture of the interstitial arterial PG, as shown by ruthenium red staining28 in this disease, is markedly disrupted. The individual ruthenium red-positive granules in the calcified zones are larger and more amorphous than in noncalcifying areas, and their association via thin filamentous threads appears disrupted. The ruthenium red-positive granules are believed to represent collapsed PG monomers, and the threadlike structures connecting adjacent granules are thought to represent hyaluronic acid as

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part of the PG aggregate.²²⁻³¹ It may be that the size and shape of the PG granules observed in the calcified region are due to the binding of calcium and/or other accessory proteins carrying calcium to the PG. The propensity of calcium to bind to PG is well documented.^{19,22,23} Furthermore, the disruption of the interconnecting network of PG in the calcified zone is consistent with the suggestion that deaggregation of PG may promote calcification.¹⁹

The finding of matrix vesicles in areas of calcification in the present study differs from that in a previous report of IIAC where the absence of these structures was noted. However, matrix vesicles were not as abundant in calcified regions examined in this study as in other calcifying tissues. The reason for this discrepancy is not clear, but the two studies may have examined tissues at different stages of calcification. The matrix vesicles may be more involved in

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promoting mineral formation once initial mineralization had occurred. 19

In summary, our report contributes new information concerning IIAC. It points out the limitations of prenatal diagnosis by ultrasonography, clarifies the mode of genetic transmission, offers an effective alternative for treating the hypertension that so often accompanies this disease, and sheds some light on the cause. The results of the ultrastructural studies indicate alterations in the PG organization in blood vessels of patients with IIAC. A determination of whether these changes predispose the vessel to calcification or result from the calcifying process awaits further study.

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Microalbuminuria in Adolescents With Insulin-Dependent Diabetes Mellitus

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 Two hundred ten adolescents aged 12 to 18 years with insulin-dependent diabetes mellitus were screened for microalbuminuria (albumin excretion rate of 15 to 300 µg/mln). Sixteen (7.6%) showed persistent microalbuminuria (mean albumin excretion rate of $70.9 \pm 56.2 \mu g/min$). There were no significant differences between those with and without microalbuminuria with respect to age, sex, disease duration, and blood pressure over the previous 9 months and hemoglobin A., level measured over the preceding 3 years. Within the group with microalbuminuria, there was no correlation between albumin excretion rate and blood pressure. However, there was a significant positive correlation between log albumin excretion rate and mean hemoglobin A_{1c} values measured over the preceding 3 years. Our findings suggest that when microalbuminuria has developed, poorer metabolic control is associated with a higher albumin excretion rate. An actual rise in systemic blood pressure may not always precede the development of microalbumin-

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Insulin-dependent diabetes mellitus (IDDM) is complicated by clinical nephropathy in 30% to 40% of patients. ¹⁻³ The earliest sign of this complication is elevated urinary albumin excretion, termed *microalbuminuria*. This may be caused by abnormal permeability of the glomerular membrane, increased glomerular perfusion pressure, or a combination of these two factors. ⁴⁻⁵ Several longitudinal studies have shown that the presence of microalbuminuria strongly predicts the progression to clinical diabetic nephropathy. ⁵⁻⁷

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The prevalence of microalbuminuria in children and adolescents with IDDM has been reported as 15% to 20% ²⁻¹¹ and is confined largely to those older than 12 years. ^{8,9} Raised systemic blood pressure (BP), poor metabolic control, and the onset of puberty have been suggested as factors that may be associated with the development of microalbuminuria but not consistently so. ⁸⁻¹⁴

We have previously reported that the albumin excretion rate (AER) derived from a 1-hour timed urine collection is a highly sensitive screen for microalbuminuria in IDDM. This study aimed at screening the adolescent population in our diabetes clinic to identify those characteristics that are associated with microalbuminuria.

PATIENTS AND METHODS

All 210 adolescents aged 12 to 18 years, attending the diabetes clinic at The Hospital for Sick Children, Toronto, Canada, were screened using a 1-hour timed urine collection while sitting at rest. The patients were screened during a 3-month period. Microalbuminuria was defined as an AER of 15 to 300 μg/min. 4,5 Those patients identified as showing positive results on the 1-hour AER were confirmed as having microalbuminuria if two 24-hour urine collections also showed an elevated AER (result of urinalysis was negative for blood). While performing the collections at home the patients were asked to avoid vigorous exercise. Urinary creatinine excretion was used to determine whether the collection was complete (normal range, 15 to 20 mg/kg per day) and it was repeated if necessary. The volume was recorded and aliquots were stored at -20° C until analysis.

Urinary albumin concentration was measured by a double antibody radioimmunoassay (Pharmacia AB, Uppsala, Sweden). Intra-assay and interassay coefficients of variation were determined for the following three urinary albumin concentrations: 2.1% and 12.1%, respectively, at low concentration (5 mg/L); 1.5% and 5.8%, respectively,

at medium concentration (25 mg/L); and 1.7% and 4%, respectively, at high concentration (55 mg/L). The AER was calculated from the albumin concentration and the volume and duration of the respective collections. Urinary creatinine level was measured with the Beckman creatinine analyzer (Beckman Instruments Inc, Brea, Calif).

Hemoglobin A_{1c} (Hb A_{1c}) was measured by high-pressure liquid chromatography after removal of the labile fraction. ¹⁶ The nondiabetic range is 4% to 6%. Each patient's Hb A_{1c} levels during the preceding 3 years were assessed, with a minimum of 3 measurements per patient per year (range, 3 to 4 measurements) and eight measurements every 5 years (range, 8 to 12 measurements). The mean values were recorded.

Blood pressure was measured by the patient's regular physician at the diabetes clinic after a rest of 10 to 15 minutes, using a standard mercury sphygmomanometer and appropriate cuff size. Diastolic BP was recorded as the disappearance of Korotkoff's sounds (phase 5). The measurements were made without knowledge of the patient's AER. The mean of three measurements taken every 3 months during 9 months was recorded. Those patients with microalbuminuria had had their BP measured every 3 months at clinic visits since diagnosis. These were plotted on age-specific percentile 7 and compared with 16 age- and sexmatched diabetic controls. They also had their BP measured every 2 minutes for 20 minutes by a Dinamap Vital Signs Monitor (Critikon, Tampa, Fla) after lying at rest for 30 minutes to establish a reliable baseline. The mean of the last 10 minutes of measurement was recorded. Retinopathy was assessed by a consultant opthalmologist by direct ophthalmoscopy after pupillary dilation and graded as background or proliferative.

The study was approved by the Humar Experimentation Review Committee of The Hospital for Sick Children.

STATISTICAL ANALYSIS

Characteristics of the groups with and without microalbuminuria were compared using Student's t test. Linear regression analysis was used to analyze the relationship of AER to BP and HbA_{1e} level, within the group with microalbuminuria. Results of the AER were not normally distributed, and therefore were analyzed after log transformation. Results are expressed as mean \pm SD unless otherwise stated.

RESULTS

Two hundred ten adolescents with IDDM (109 girls, 101 boys) aged 12 to 18 years (mean \pm SD, 14.9 \pm 1.8 years) were screened, of whom 32 patients had a raised AER on the 1-hour timed urine collection. Of these, 16 also showed a raised AER on both 24-hour urine collections, 12 showed a normal AER on both 24-hour urine collections, and 4 showed a raised AER (19 to 60 μ g/min) on one of the two 24-hour urine collections. These 4 patients with an intermittently raised AER were not included in the group with microalbuminuria for the purpose of this study.

In the 16 patients (7.6%) (9 female, 7 male) who showed presence of microal-buminuria on the 1-hour urine collection and two 24-hour urine collections, the mean AER of the 24-hour collections was 70.9 ± 56.2 µg/min (median, 51.4 µg/min; range, 16.3 to 210 µg/min). Twelve of these 16 patients provided a third 24-hour collection which confirmed persistent microalbuminuria.

Of interest, 7 (44%) of the 16 patients with microalbuminuria were noted to be of Greek descent, as compared with 19 (10%) of the 194 patients without microalbuminuria (P<.001).

The Table shows the clinical and biochemical characteristics of patients with and without microalbuminuria. There were no significant differences between the groups with and without microalbuminuria in terms of age $(14.5\pm1.9 \text{ and } 14.9\pm1.7 \text{ years, respectively})$, sex distribution, and disease duration $(5.7\pm3.3 \text{ and } 5.5\pm3.6 \text{ years, respectively})$.

Mean BP, measured at 3-month intervals during the previous 9 months, did not differ between the groups with and without microalbuminuria ($115/74\pm12/7$ and $115/74\pm8/6$ mm Hg, respectively) (Table). There was no significant change in BP during the preceding 9 months in either group. However,

Clinical and Biochemical Characteristics of the Groups With and Without
Microalbuminuria*

	Nonmicroalbuminuric Patients (n = 194)	Microalbuminuric Patients (n = 16)
Age, y	14.9±1.7	14.5±1.9
Sex, M:F	94:100	7:9
Disease duration, y	5.5 ± 3.6	5.7 ± 3.3
Blood pressure†	115/74 ± 8/6	115/74±12/7
HbA, over 1 year, %	8.8±1.3	8.7 ± 1.1
HbA _{se} over 3 years, %	8.8 ± 1.0	8.6 ± 1.3
Retinopathy Background	10 (5.1%)	2 (12.5%)
Proliferative	1	0

^{*}Results are expressed as mean ± SD.

8 of the 16 patients with microalbuminuria showed a small increase in diastolic BP (14±3 mm Hg) within the normal range17 when all clinical BP readings since diagnosis of IDDM were reviewed and tracked on age- and sex-specific percentiles. Systolic BP showed no consistent trend. The 16 age- and sexmatched controls showed no increase in BP since diagnosis of IDDM. No patient had hypertension, but an 18-year-old girl with microalbuminuria had BP readings at the 90th to 95th percentiles for age (130/80 to 85 mm Hg).17 In the group with microalbuminuria, there was no significant correlation between log AER and BP, both when measured at 3-month intervals during the preceding 9 months and at 2-minute intervals by the Dinamap monitor during a 20minute period (mean of the last 10 minutes recorded was 112/66+10/11 mm Hg).

The mean $\mathrm{HbA_{1c}}$ did not differ between those with and without microal-buminuria during the preceding 1 (8.7% \pm 1.1% and 8.8% \pm 1.3%, respectively) and 3 years (8.6% \pm 1.3% and 8.8% \pm 1.0%, respectively). In addition, within each group, the 1- and 3-year mean $\mathrm{HbA_{1c}}$ levels did not differ. However, in the group with microalbuminuria there was a positive correlation between log AER and mean $\mathrm{HbA_{1c}}$ values measured every 3 months during both the preceding 1 and 3 years (r=.63, P=.009 and r=.52, P=.04, respectively) (Figure).

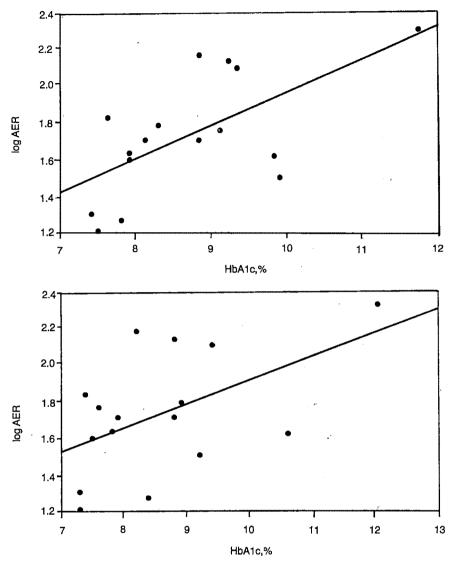
There was no significant difference in the prevalence of diabetic background retinopathy in the two groups (10/194 patients [5.1%] without microalbuminuria; 2/16 patients [12.5%] with microalbuminuria; P=.10). One patient, who did not have microalbuminuria, had proliferative retinopathy.

COMMENT

We found a relatively low prevalence of microalbuminuria of 7.6% in our adolescent population with IDDM. Previous smaller studies have shown a 15% to 20% prevalence in late childhood and adolescence,811 with microalbuminuria being largely confined to those older than 12 years. Several of these studies used only one collection to detect a raised AER⁹⁻¹¹ and, therefore, may include patients with intermittent microalbuminuria. Prevalence of microalbuminuria in our patients is consistent with that in patients with a similar disease duration in a recent comprehensive study. 18

Intermittent microalbuminuria is thought to precede persistent microalbuminuria early in the course of diabetic nephropathy. 14,19 We identified four patients who showed a raised AER on only one of two 24-hour collections and they were excluded from the group with persistent microalbuminuria. Follow-up of these individuals is warranted to assess whether persistent microalbuminuria develops and when. Twelve patients with a raised 1-hour AER had a normal 24-hour AER. This was consistent with our findings that the 1-hour screening test has a predictive value of 53% for a positive result and 96% for a negative result.15 The high prevalence of microalbuminuria in children of Greek descent

[†]Measured every 3 months during a period of 9 months.



Correlation between log albumin excretion rate (AER) and mean hemoglobin A_{1c} (Hb A_{1c}) values measured every 3 months during the preceding 1 (top) and 3 (bottom) years.

with IDDM is interesting though not readily explained.

It is important that our patients with a raised AER had a relatively short duration of disease. Other studies have described a mean time of at least 7 years before microalbuminuria develops. ⁸⁻¹¹ While patient numbers in the group with microalbuminuria are small in all these studies, it is relevant to any screening program that, in this age group, changes may be seen within 3 to 5 years of diagnosis.

We could find no difference in metabolic control between the groups with and without microalbuminuria as assessed by mean HbA_{1c} levels during the previous 1 to 3 years. Hemoglobin A_{1c}

levels were noted to be stable in that neither group showed any change in mean HbA_{1c} levels during the preceding year, compared with the preceding 3 years. Our findings extend those of other studies in which only a single HbA_{1c} measurement was evaluated. Another recent study evaluating long-term diabetic control saw this to be a major risk factor in the development of microalbuminuria. However, their patients had had IDDM for a longer period and the effect of metabolic control on the prevalence of microalbuminuria increased with duration of disease.

Within our group with microalbuminuria, a higher AER was associated with higher HbA_{1s} levels over the preceding 1

and 3 years. This association parallels recent prospective studies suggesting that improvement in metabolic control may have a beneficial effect on microal-buminuria. ²⁰⁻²² It is possible that given a predisposition to develop nephropathy, poorer metabolic control accelerates the rise in albumin excretion but is not an essential initiating factor. Blood pressure or other hereditary factors may be important. ²³

Interestingly, systemic BP measured during the preceding 9 months did not differ between the groups with and without microalbuminuria, without any change during this time interval. However, 50% of the patients with microalbuminuria showed a small rise in diastolic BP over time since diagnosis. The relationship of this rise to the onset of microalbuminuria could only be determined by a prospective study. There was no correlation between BP and AER within the group with microalbuminuria. Higher BP levels have been seen in patients with microalbuminuria without renal impairment, 8,9,12,18 but not invariably so 10,14 and frequently assessment has been made on one measurement alone.8-10,13 A distinction between lower and higher AERs within the microalbuminuric range has been made, with higher BP levels being confined to AERs above 30 μ g/min¹² or 70 μ g/min.¹⁸ Twelve of our 16 patients had an AER less than 70 µg/min, which may explain the normal BP levels in our group.

It is well recognized that hypertension causes a more rapid progression of both incipient and established diabetic nephropathy,4,5 and this progression may be controlled with antihypertensive therapy. 24-27 However, recent literature has suggested that even a predisposition to hypertension is a risk factor for diabetic nephropathy, and that hypertension is not simply a consequence of diabetic nephropathy but an important contributing factor.28-30 Our data suggest that an actual rise in systemic BP does not always precede or initiate the development of microalbuminuria. It is possible that a rise in intraglomerular pressure initiates the renal lesion well before systemic hypertension is recognized. This possibility forms the basis for attempts at decreasing intraglomerular pressure and hence albuminuria, using angiotensin-converting enzyme inhibitors.²⁴ The use of these agents in microalbuminuric, normotensive children with IDDM is the subject of another report. Our findings also emphasize the need for a prospective study of BP trends and possible markers of a predisposition to hypertension²⁵⁻³² in early IDDM to clarify the timing of its role in diabetic nephropathy.

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Law of Small Numbers: 2+2=5 (For sufficiently large values of 2.)

"Even though the moon is 1/49 the size of the earth, it is a lot further away."

Ernie Kovaks

Barker's Proof: Proofreading is more effective after publication.

Fundamental Rules of Writing, Editing, and Publishing

- 1. Don't use no double negative.
- 2. Make each pronoun agree with their antecedent.
- 3. Join clauses good, like a conjunction should.
- 4. About them sentence fragments.
- 5. When dangling, watch your participles.
- 6. Verbs has to agree with their subjects.
- 7. Just between you and I, case is important too.
- 8. Don't write run-on sentences they are hard to read.
- 9. Don't use commas, which aren't necessary.
- 10. Try to not ever split infinitives.
- 11. Its important to use your apostrophe's correctly.
- 12. Proofread your writing to see if you any words left out.
- 13. Correct spelling is absolutely essential.
- 14. Don't abbr.
- 15. You've heard it a million times: avoid hyperbole.

Persistent Perceptions of Vulnerability Following Neonatal Jaundice

Kathi J. Kemper, MD, MPH; Brian W. Forsyth, MD, ChB; Paul L. McCarthy, MD

• Treatments for neonatal jaundice are generally considered both safe and effective. We hypothesized that such treatments would be associated with symptoms of the vulnerable child syndrome. persisting up to 6 months. Mothers of otherwise healthy infants who had jaundice and demographically similar infants without laundice born at Yale-New Haven (Conn) Hospital were surveyed and compared 6 months after discharge from the hospital. By 6 months, the infants with jaundice had significantly more feeding difficulties, eg, they were less likely to be breast-feeding. Unexpectedly, the mothers of Infants with jaundice switched from being less likely to leave their Infants with someone else at 1 month to leaving the infants significantly more than mothers of Infants in the comparison group. Although the mothers of infants in the comparison group reported a similar number of Infant health problems, the mothers of infants with jaundice were more likely to judge the problems as serious and to have taken the infant to an emergency department. The benefits of treating jaundice in otherwise healthy infants should be weighed against the risks of developing the vulnerable child syndrome.

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The vulnerable child syndrome was originally described in families in which the parents believed that their child had suffered a "close call" and thereafter was perceived as vulnerable to serious injury or accident. The vulnerable child syndrome is a well-known consequence of several problems that occur in newborns. 24 Because mothers

tend to view their child's medical condition as more serious than pediatricians do¹⁸ and may misinterpret or misunderstand medical information, the vulnerable child syndrome is an important potential iatrogenic complication of minor illnesses and "nondisease" as well as of life-threatening disorders. Furthermore, its impact on behavior may confound the results of studies on the long-term consequences of newborn conditions, eg, behavioral disabilities resulting from moderate hyperbilirubinemia.

In an earlier portion of this study regarding maternal reactions to their infants' jaundice and its treatments, we found that (1) a majority of mothers did perceive jaundice as a serious condition even a month after discharge; (2) these mothers were at increased risk for having breast-feeding interrupted in the hospital and of completely stopping breast-feeding within the first month of life; (3) these mothers were less willing to separate from their infants; and (4) these mothers were more likely to perceive their infants' other health problems as serious and were significantly higher users of health care compared with mothers of infants who did not have jaundice.12 We continued the study to determine if these maternal behaviors, consistent with early manifestations of the vulnerable child syndrome, persist for the first 6 months of the infant's life.

SUBJECTS AND METHODS

We performed a prospective comparison cohort study of mothers of infants born at the Yale-New Haven (Conn) Hospital from February 1987 through February 1988. Mothers of infants who had jaundice were eligible if their infants had a total serum bilirubin level higher than 205 µmol/L measured prior to discharge from the hospital; mothers of infants in the comparison group were excluded

if their infants had bilirubin determinations at any time up to 1 month of age. Mothers in either group were excluded if their infants weighed less than 2500 g or had spent more than 6 hours in the intensive care nursery.

Mothers who agreed to participate completed a baseline questionnaire in the hospital prior to discharge to assess initial maternal attitudes and comparability between groups. Written follow-up questionnaires were mailed to mothers 1 month and 6 months after discharge to ascertain maternal attitudes and behaviors toward their infants. To increase the response rate, nonrespondents were reminded by telephone (when available) and remailed questionnaires up to two times. One-month outcomes have been reported previously.¹²

Four major outcomes were assessed at 6 months: (1) infant feeding; (2) maternal perceptions of infant temperament, according to the Bates' Infant Characteristic Questionnaire¹⁸; (3) separation-bonding difficulties, ie, willingness to leave the child with another caretaker (including the father); and (4) perceptions of infant health and health care use. High health care use was arbitrarily defined as taking the child for more than four well-child check-ups or more than two sick visits, or as any visit to the emergency department other than for bilirubin determinations.

Results were analyzed for mothers completing both questionnaires. Statistical analyses were performed using the χ^2 test for nominal variables, the Mann-Whitney U test for categorical variables, and the Student t test for continuous variables. Discriminant function and multiple regression analyses were performed to control for potential confounders and effect modifiers.

RESULTS

Of those who completed the 1-month questionnaire, 63 (74%) of the 85 mothers of infants with jaundice and 69 (56%) of the 124 mothers of infants in the comparison group also completed the 6-month follow-up questionnaire. Nonrespondents to the 6-month questionnaire

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Table 1.—Jaundice and Comparison Groups at Baseline Group Characteristics Jaundice, No. (%) Comparison, No. (%) Maternal variables 29.2 29.4 Age, v Race, W/total 55/63 (88) 60/69 (87) MD, clinic/total 4/63 (7) 2/69 (3) 42/63 (67) 36/39 (52) Primiparous Mean trait anxiety score 34.3 33.7 Plenty of help at home 55/63 (87) 55/69 (80) 43/69 (62) Life stress in last 6 mo 34/63 (54) Infant variables 3424 3510 Birth weight, g Gestational age, wk 39.0 39.9* 6.0 5.8 Age at follow-up, mo Initial feeding of breast milk 46/63 (73) 47/69 (68) Breast-feeding interrupted in hospital 7/46 (15) 0/47*

^{*}P<.05.

	Group		
Outcomes	Jaundice, No. (%)	Comparison, No. (%)	
Feeding Still breast-feeding	8/46 (17)	15/47 (32)	
Elemental formula	6/63 (10)	1/69 (1)*	
No. of formulas, mean	2.1	1.6*	
Temperament, mean scores† Fussy	17.0	16.1	
Unadaptable	8.2	8.9	
Dull	5.7	6.4	
Unpredictable	7.7	8.1	
Separation Once or twice since birth	4/63 (6)	2/69 (3)	
48 h or longer	11/63 (17)	4/69 (6)*	

^{*}P<.05

†Standard normal scores for 6-month-old infants on the Bates Infant Characteristic Questionnaire are fussy 17.8: unadaptable, 8.9: cull, 5.9: and unpredictable, 7.3.

were significantly more likely to be non-white (23% [18/77] vs 12% [16/132] who were white; P<.05), have less education (58% [45/77] vs 76% [100/132] who had some college; P<.01), and be under the care of a clinic physician (16% [5/77] vs 6% [21/132] with private physicians; P<.05). No significant differences were evident between respondents and non-respondents in terms of 1-month outcomes (in relation to breast-feeding, separation, and health care use).

At baseline (Table 1), the jaundice and comparison groups were similar both demographically and in terms of risk factors for the vulnerable child syndrome. Mothers in both groups were predominantly in their late 20s, white, patients of physicians in private practice, reporting similar amounts of life stress in the 6 months since the infants' births, and with low-moderate scores on the Spielberger Anxiety Scales.14 Of all the baseline comparisons, the only differences were that the group of mothers with infants with jaundice had a higher proportion of primigravidas, had a slightly lower mean gestational age, and had a greater likelihood of having had breast-feeding interrupted temporarily during their hospital stay. The jaundiced infants had a mean peak bilirubin level of 265 µmol/L; phototherapy was used to treat 35 (56%) of 63 infants.

Infant Feeding

By the 6-month follow-up visit, fewer mothers of infants with jaundice compared with mothers of comparison infants were still primarily breast-feeding (17% [8/46] vs 32% [15/47] of those who had started; P<.05) (Table 2). Mothers of intants with jaundice were more likely to have tried an elemental formula than were mothers of comparison infants (10% [6/63] vs 1% [1/69]; P<.05), and on average they had tried a significantly greater number of different formulas (2.1 vs 1.6; P=.02) than had the mothers in the comparison group.

Temperament

No substantial or significant differences were observed between the jaundice and comparison groups on any of the four factors of the Bates' Infant Characteristic Questionnaire (Table 2). The mean scores for both groups were within the normal, standardized ranges; ie. neither group was perceived as especially "difficult" by their mothers. By 6 morths, mothers of infants with jaundice and those of comparison infants also had similar scores on the Forsyth Child Vulnerability Scale (18.9 vs 18.4; not significant [NS])16 and did not report being more worried than mothers in the comparison group that their infant "might not make it" (10% [6/63] vs 14% [10/59]).

Separation

A similar proportion of mothers in both groups reported being moderately to very anxious about leaving their infan with anyone else (22% [14/63] of mothers of infants who had jaundice vs 25% [17/69] of mothers of infants in the comparison group) (Table 2). Although at I month the mothers of infants with jaundice had more trouble separating from their infants, 12 by 6 months, nearly all mothers in both groups had left their infents at least once or twice for over an hour. Unexpectedly, by 6 months the mothers of infants with jaundice were willing to separate from their infants for much longer periods than the mothers of infants in the comparison group (P < .05by Mann-Whitney U test). For example, 17% (11/63) of the mothers of infants with jaundice had left their infants with someone else for 48 hours or longer vs

Table 3.—Health Concerns and Utilization			
	Group		
Concerns and Behaviors	Jaundice, No. (%) (N = 63)	Comparison, No. (%) (N = 69)	
Any illness	40 (63)	40 (58)	
Moderate-serious illness	18 (29)	3 (4)*	
>4 well-child visits	32 (51)	29 (42)	
>2 sick visits	15 (24)	13 (19)	
Any emergency department visit	11 (17)	5 (7)†	

*P<.05. †P = .07.

6% (4/69) of the mothers of infants in the comparison group (P<.05). These "extreme" behaviors (either not leaving the infant with someone else more than once or leaving the infant for more than 48 hours) were reported by 24% (15/63) of the mothers of infants with jaundice vs 9% (6/69) of the mothers of comparison infants (P < .05).

Health

Although a similar proportion of mothers in each group reported that their infants had had a health problem besides jaundice in the first 6 months of life (63% [40/63] in the group with jaundice vs 58% [40/69] in the comparison group), mothers of infants with jaundice were more likely to believe these illnesses (such as upper respiratory congestion, ear infections, and rashes) were moderately to very serious (29% [18/63] in the jaundice group vs 4% [3/69] in the comparison group; P < .05) (Table 3).

By 6 months, infants in each group had received the same number of immunizations (mean, 2.5 in each group), but the mothers of jaundiced infants were more likely than mothers of comparison infants to have taken their infants for (1) more than four well-child visits (51% [32/63] vs 42% [29/69]; NS); (2) more than two sick visits (24% [15/63] vs 19% [13/69]; NS); and (3) any visit to an emergency department, excluding visits for bilirubin determinations (17% [11/63] vs 7% [5/69]; P = .07). Interestingly, the mothers whose infants had been treated with phototherapy had the highest rate of health care use.

Controlling for Confounders

Because some of these outcomes could be influenced by factors other than jaundice, we analyzed the associations between the behavioral outcomes (eg, infant feeding) and jaundice, controlling for baseline variables that differed between groups and were also associated with a study outcome. For example, the lower the infant's gestational age at birth, the more likely a mother was to try a number of different formulas and to have higher health care use; lower gestational age was also more common in the infants with jaundice. However, even controlling for potential confounders (eg. infant's gestational age and birth weight, mother's parity, and the amount of help at home) in a regression analysis, jaundice remained strongly associated with the number of formulas a mother had tried for her infant (P < .05), the use of special formulas (P < .01), and emergency department visits (P < .02).

COMMENT

The results of this study extend our earlier findings that neonatal jaundice and our treatments for it are associated with an increased risk of maternal behaviors consistent with the vulnerable child syndrome. Current treatments for jaundice, such as temporarily interrupting breast-feeding and the use of phototherapy (involving some separation of mother and infant), are reported to be upsetting to mothers and to imply that their infants' conditions are moderately to very serious.12

Consistent with others' research, we found that early interruption of breastfeeding and supplementation with formula predisposed toward premature termination of breast-feeding.15-17 The decrease in breast-feeding observed at 1 month in association with in-hospital interruption of breast-feeding persisted at 6 months. This should be considered an important risk of current management, since premature termination of breast-feeding may increase the risk of respiratory and gastrointestinal illnesses and lead to higher rates of outpatient visits, hospitalization, and health care costs. 18,19

Not only did the mothers of infants who had jaundice more readily give up breast-feeding, but they also tried a greater number of formulas, especially special formulas. The findings of Forsyth et al suggest that frequent formula changes are associated with (1) maternal beliefs that the cause of the infant's feeding problems are intrinsic to the child, (2) an increased perception of infant vulnerability, (3) behavior problems, and (4) higher health care use persisting 31/2 years. The early feeding problems observed in this study are another indication of the developing vulnerable child syndrome.

Mothers of both infants with jaundice and comparison infants tended to see their infants as relatively easy to care for and reported a similar number of other infant problems and concerns. Their scores on the Forsyth Vulnerability Scale21 were not significantly different, perhaps because it was designed for use with older children. Certain items on the scale, such as "my child seems to have more accidents and injuries than other children" or "I often have to keep my child indoors because of health reasons," may not be appropriate for detecting perceived vulnerability in 6month-old infants. Maternal concerns may also be more subtle than reporting the worry that the infant "might not make it." Further refinement is required in developing scales to assess conscious and unconscious parental fears about infant vulnerability in the first year of life.

The change in separation behavior in the mothers of infants with jaundice from reluctance to leave their infants with anyone else at 1 month to being much more willing to leave them for 2 days or more by 6 months was unexpected. It is difficult to determine from our data when or why these mothers made the switch from one extreme in separation behavior to the other. To understand better the risks for and development of the vulnerable child syn-

drome and attachment disorders, it is important to explore further these differences in separation behaviors.

The marked differences in health care use observed at 1 month had begun to diminish by the 6-month follow-up. It is tempting to speculate that by 1 or 2 years, health care use would be the same in the infants with jaundice and the comparison infants. But other evidence suggests that early patterns of health care use may persist.22,23 Although a child may be vulnerable to illness and require health care for biologic reasons (eg, extreme prematurity), social causes (eg, single, young mother), or inherent psychological causes (eg. blood pressure reactivity to stress in some children),24 perceived vulnerability may be an equally important predictor.25 Later health care use may also be affected by displaced maternal concerns about a child's feeding and nutrition or separation difficulties. More research is needed to sort out how these factors interact and whether later adverse events can renew or evoke early maternal perceptions of vulnerability.

Although the observed differences occurred in the expected directions, several did not reach statistical significance. The sample size for the 6-month follow-up was too small for adequate

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statistical power for some comparisons.26,27 and nonrespondents to the 6month follow-up tended to be in nonwhite clinic patients with minimal education, potentially biasing the results toward underestimation of the effects of jaundice. The comparison group also reported being less interested in completing the 6-month questionnaire; yet despite the potential for bias due to nonresponse, demographic variables were surprisingly similar in the groups of mothers of infants with jaundice and the mothers of comparison infants who did respond. It is possible that the study itself served as a source of anxiety and increased perceptions of vulnerability in the mothers of infants who had jaundice. However, several mothers of infants with jaundice wrote to express their gratitude for being able to voice their concerns and for the support they felt from the investigators during their "difficult time."

After years of study, no good evidence has established that treating moderate jaundice in an otherwise healthy term newborn provides any long-term benefits for the treated child.28 Rather, we have routinely adopted fairly aggressive preventive therapies because they have been seen as potentially beneficial (extrapolating

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from sick premature infants with jaundice and those suffering from severe hemolytic disease), harmless, and relatively inexpensive. However, if the risks of temporarily interrupting breast-feeding are early termination of breast-feeding and the implication that the infant may have problems with regular milk formulas, these risks should be weighed against the benefits of a somewhat speedier decline of modestly elevated bilirubin levels. Before beginning treatment, we need to assess carefully our abilities to reassure a mother that her infant is basically healthy and to support and encourage her ability to care for "minor" problems.29 If taking the infant away from mother's arms to place him or her under phototherapy lights and doing frequent blood tests result in a pattern of separation difficulties and/or high health care use characteristic of the vulnerable child syndrome, we need to add these risks to the cost of prolonged hospitalization and repeated laboratory measurements in assessing the relative value of treatment.

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Urinary Tract Symptoms and Urinary Tract Infection Following Sexual Abuse

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 During a routine follow-up visit, 428 victims of sexual abuse and their caretakers were asked about genitourinary complaints. Symptoms elicited included vaginal pain, increased urinary frequency, dysuria, and enuresis. A urinalysis was performed for all victims with symptoms, and those with positive or equivocal urinalysis results had a urine culture done. Urinalysis and urine culture were performed on a control group of 53 consecutive asymptomatic victims. Twenty percent (85/428) of the victims complained of one or more genitourinary symptoms. The most common symptom was vaginal pain (51%). Of the symptomatic victims, only 2 had a urinary tract infection. None of the 53 asymptomatic control victims had a urinary tract infection. There was no significant relationship between the presence of genitourinary symptoms and repetitive abuse, genital trauma, vaginal contact, or gender of the victim. However, patients younger than 6 years of age were more likely to have genitourinary symptoms than older patients. These findings indicate that urinary tract symptoms following sexual abuse are common but that urinary tract infection is quite uncommon. Our study does not support routine screening of children for urinary tract infection solely because they have been sexually abused.

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Sexual activity has been associated with an increased frequency of urinary tract infection (UTI) in adolescents and young adults. Frequent or recurrent UTI has been described as a feature of sexual abuse, but this association has not been well documented. Recently, a stronger association has been suggested, implying that UTI may be an indicator of sexual abuse. However, the study by Reinhart found the prevalence of UTI in victims of sexual abuse to be no greater than that in populations of healthy schoolchildren.

The current study was designed to

answer two questions. First, What is the frequency of urinary tract symptoms following sexual abuse? Second, What is the frequency of UTI in sexually abused children?

PATIENTS AND METHODS

Thomas Jefferson University Hospital (Philadelphia, Pa) is a sexual-assault center for Philadelphia County, Pennsylvania. The sexual-assault center is one of two hospital-based facilities designated to serve as crisis evaluation and treatment centers for sexually abused children. Victims are referred from the police, private physicians, hospital emergency departments, social service agencies, and rape-counseling centers throughout the city. Self-referrals are also common.

The subjects for the study underwent routine initial and follow-up examinations. At the time of the initial complaint of sexual abuse, an initial examination was performed by pediatric residents and by nurses who are experienced in the examination of abused children. The history obtained included duration of abuse, alleged perpetrator, and the type of sexual contact. A physical examination was performed, evidence was collected, and specimens for bacterial cultures were obtained from oral, anal, and vaginal sites. Serologic tests for syphilis (rapid plasma reagin card test) were also performed. Presence or absence of genital trauma-such as vaginal lacerations, scars, or increased hymenal orifice size-was specifically noted. Signs of infection such as vaginal discharge, condylomata, or vesicles were also recorded.

Victims were then seen in a follow-up clinic 1 to 3 weeks after the initial report of sexual abuse. During this routine visit, victims and their caretakers were asked about a variety of somatic and behavioral problems, including questions about genitourinary (GU) symptoms. We asked specifically about the following symptoms: vaginal pain, increased urinary frequency, dysuria, and enuresis. All victims symptomatic with GU complaints had a urinalysis performed on a midstream, clean-catch specimen. The urinalysis included a dipstick for nitrites and a microscopic examination. Those with abnormal results of urinalysis (>10 white blood cells [WBCs] per high-power field [hpf] in a spun urine sample, more than 2 bacteria per hpf, or a positive nitrite test) or an equivocal result (between 5 and 10 WBCs per hpf in a spun urine sample, or 2 bacteria or more per hpf) had a urine culture done using a dip-slide method (Uricult, Medical Technology Corp, Somerset,

NJ). A control group was created, because asymptomatic victims rarely had either a urinalysis or urine culture performed. The control group consisted of 53 consecutive asymptomatic victims. All members of the control group had a urinalysis and a urine culture performed on a midstream, clean-catch specimen. Data from symptomatic victims were collected from March 1980 to September 1988, while data for the asymptomatic control group were collected from March 1987 to September 1988. The asymptomatic control group appeared to be a representative sample of all asymptomatic victims. No significant differences were found between the control group and all other asymptomatic victims with respect to the victim's age, gender, relationship to the perpetrator, the frequency of physical findings, and the type and duration of the abuse. Data were analyzed primarily using descriptive methods, as well as Student's t test for interval data and χ^2 for comparing categorical data.

RESULTS

A total of 428 sexual-abuse victims were cared for in the follow-up clinic during the period of the study. The mean age of the victims was 8.6 years (SE=0.18 years). The range of ages was from 1 to 16 years. Eighty-four percent of the victims were female and 67% were black.

Eighty-five (20%) of the victims complained of one or more GU symptoms at the time of the follow-up visit. The most commonly reported symptom was vaginal pain, reported by 51% of the symptomatic children. Recent onset of diurnal or nocturnal enuresis was reported by 28% of the symptomatic victims. Dysuria and urinary frequency were reported by 25% and 24% of the symptomatic victims, respectively (Table 1). Fourteen (16%) of the 85 symptomatic victims had two GU symptoms and 5 (6%) symptomatic children reported three symptoms. Fifty-two of the symptomatic children had become symptomatic since their initial examination; 33 had described symptoms at the time of the initial examination that had persisted at follow-up. Only two asymptomatic control patients reported symptoms at the initial examination.

All symptomatic victims had a urinalysis but only 32 had a urine culture ob-

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Table 1.—Genitourinary Tract Symptoms Reported Among Symptomatic Sexually Abused Children (n = 85)

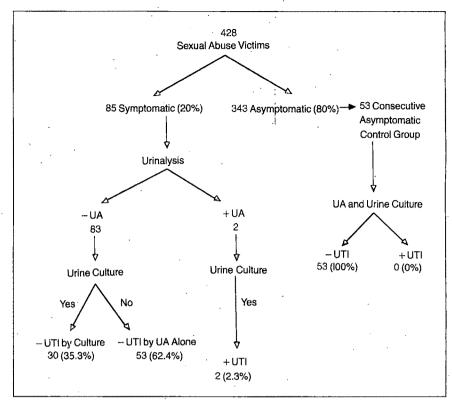
Symptom	No. (%) of Symptomatic Victims Reporting
Vaginal pain	43 (51)
Enuresis	24 (28)
Dysuria Increased urinary	21 (25)
frequency	. 20 (24)

tained at the follow-up visit. Of the 85 symptomatic victims, only 2 had a UTI as diagnosed by urinalysis or culture. These 2 girls had greater than 10 WBCs per hpf, greater than 2 bacteria per hpf, a positive nitrite test, and a urine culture with more than 10⁵ organisms per milliliter of urine. These 2 girls had neither prior UTI by history nor evidence of other concurrent GU infection. Fiftythree asymptomatic control patients underwent urinalysis and urine culture, but none were found to have a UTI (Figure).

Factors that might be related to the reporting of symptoms such as genital trauma (including genital infection), a history of vaginal contact, or repetitive abuse were analyzed. A χ^2 analysis did not show a significant relationship between the presence of genital trauma and the presence of GU symptoms. Similarly, a significant relationship was not found between a history of vaginal contact or repetitive abuse and the presence of GU symptoms (Table 2). Because vaginal pain was the most commonly reported symptom, female subjects were more likely to be symptomatic. However, when the genderspecific symptom of vaginal pain was removed from the analysis, the proportion of female subjects who were symptomatic was not different from the proportion of male subjects who reported symptoms. When the effect of age on the presence of GU symptoms was examined, we found that victims younger than 6 years old were significantly more likely to complain of GU symptoms than older victims (Table 2). Furthermore, the mean age of symptomatic victims was 6.9 years, significantly less than the mean age of 9.0 years of all asymptomatic victims (t test = -4.75, P < .0005).

COMMENT

The findings in this study indicate that urinary tract symptoms following



Study flowsheet findings of the sexual-abuse victims. UA indicates urinalysis; UTI, urinary tract infection.

Factor Present	Symptomatic No. (%) (n = 85)	Asymptomatic No. (%) (n = 53)	χ2
Genital trauma	38 (45)	17 (32)	2.05
Vaginal contact	47 (55)	25 (47)	1.11
Repetitive abuse	44 (52)	26 (49)	0.12
Age, <6 y	44 (52)	12 (23)	12.68

*P<.05 (not significant) †P<.0005.

sexual abuse are common, reported by 20% of the victims in our population. In contrast, UTI was not common. Only two symptomatic victims and no asymptomatic child was found to have a UTI.

There are at least two explanations for the finding of a high prevalence of GU symptoms without an associated high prevalence of UTI. One option is that the symptoms are psychosomatic in origin. Our results support this conclusion by showing that the GU symptoms were not associated with either a history of vaginal contact or with the victim's gender. Several studies have also shown that sexual abuse victims frequently report somatic complaints without an organic basis. Such symptoms reported include "stomachaches," headaches, encopresis, and enuresis. 68

Rimza et al⁹ reported that 67% of abuse victims as compared with 36% of control patients had somatic or behavioral problems without demonstrated organic cause. Genitourinary symptoms were the somatic complaints most commonly reported, elicited from 29% of the victims.⁹ Similar to our finding, victims younger than 6 years old were the most likely to report symptoms.⁹ Thus, it is possible that the large number of victims with GU symptoms, but with no UTI, may be manifesting a psychosomatic disturbance due to the abuse.

A second explanation for the lack of UTI in most of the symptomatic children is that an organic cause for the symptoms was present but was not found. For this to be an acceptable hypothesis, the cause would have to be

missed by urinalysis and by urine culture. Urinalysis was performed in all symptomatic victims, but urine culture was performed in only 38% (32/85). All 53 children with symptoms for whom urine cultures were not submitted had urine specimens with fewer than 5 WBCs per hpf, fewer than 2 bacteria per hpf, and a negative nitrite test. A UTI could be present in the absence of leukocyturia and without a positive nitrite test; however, the absence of significant bacteruria makes an infection unlikely. Scattered bacteria correlate with colony counts of 10° to 104. If the colony count is 10° or greater, sheets of bacteria are seen in almost every field.10

Prophylactic antibiotics for sexually transmitted diseases are sometimes given to sexual abuse victims. These antibiotics might alter the progression of symptoms or the culture results in children who received them. Only 23 (27%) of the 85 symptomatic follow-up group victims and 7 (13%) of the 53 asymptomatic controls received prophylactic antibiotics at the time of their initial examination. The proportion of symptomatic children who had received prophylactic antibiotics was the same regardless of whether they reported symptoms at the initial visit (10 [30%] of 33) or had no symptoms initially (13 [25%] of 52). No child received phenazopyridine hydrochloride (Pyridium) or other specific symptomatic therapy. Both of the children with identified UTIs had positive cultures at follow-up despite their having received prophylactic antibiotic therapy at the initial visit. No clear effect of the prophylactic antibiotic therapy was demonstrated; however, the infrequent antibiotic use was not expected to have a very significant effect.

Chlamydia trachomatis infection could be considered as a possible cause for the reported symptoms. Rectogenital chlamydial infection has been identified in 4% to 17% of sexually abused children when these children had routine cultures for the organism.11-18 However, most young children with C trachomatis vaginal infection are asymptomatic. 11,12,14 Chlamydia trachomatis has been reported to be a cause of "acute urethral syndrome" that results in the symptom of dysuria alone without urgency or frequency. This syndrome has been reported in young women15 and in adolescent females,16 but it is not

known if it occurs in young children. Importantly, it is unusual for those women who have chlamydial infection as a cause for their dysuria to have normal results of urinalysis. Most of these female subjects have significant pyuria on urinalysis.15 Adolescent boys with chlamydial urethritis are usually clinically asymptomatic, but significant pyuria is typically present.17 We did not routinely take cultures from either the symptomatic or the asymptomatic victims for Ctrachomatis and it is certainly possible that we may have missed several cases of chlamydial urethritis as a cause of dysuria reported by the victims. Except for the two children with documented UTI, none of the symptomatic children had significant pyuria. Five symptomatic children had vaginal discharges, but all had negative cultures for C trachomatis. Most chlamydial infections in children and many in adolescents are asymptomatic. However, it is not known whether pyuria or a discharge must be present in the child with an atypically symptomatic chlamvdial infection.14

Another cause of GU tract symptoms that may elude diagnosis is UTI with Staphylococcus saprophyticus. Staphylococcus saprophyticus is a coagulasenegative staphylococcus believed to be the second leading cause of acute UTI in young women.18 It has recently been reported as the cause of a UTI in a sexually abused child. 19 Most patients with S saprophyticus UTI are symptomatic with dysuria. Pyuria is almost universally present and hematuria is found in approximately two thirds of the patients. 18 Staphylococcus saprophyticus will not cause a positive nitrate test because the organism does not reduce nitrate. It will grow well on the agar pad (Uricult CLED), but the MacConkey agar pads support growth of the organism unreliably.18 One of the pitfalls in making the diagnosis of S saprophyticus UTI is that frequently less than 106 organisms per milliliter of urine are grown in culture due to the clusterforming tendency of staphylococci.20 Thus, although it is possible that some of the symptomatic victims had a UTI with S saprophyticus, it is unlikely that the urinalysis would have been negative for pyuria or hematuria in most cases.

In conclusion, this study shows that while GU tract symptoms are common following sexual abuse, UTI is quite uncommon. The widely held perception that UTI is common in sexually abused children may be due to erroneously equating dysuria with UTI. Obtaining a urine culture in sexually abused children with GU symptoms is a reasonable action and culturing specifically for C trachomatis and S saprophyticus may be helpful. However, our study does not support routine screening of children for UTI solely because they have been sexually abused.

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When Is a Test Result Abnormal?

Defining Limits and Risks

Joel Charrow, MD, Larry V. Hedges, PhD

· Test results from "normal" and "nonnormal" individuals frequently overlap. Individuals with test results near the region of overlap have a high risk of being misdiagnosed. We present a statistical method for quantifying the certainty of diagnoses and defining a normal range, and illustrate its application with a specific example from a Tay-Sachs disease carrier screening program. This method can be applied to any test result based on a continuous variable and is particularly well suited to screening programs where the risk or incidence of a disease is known. We use an inconclusive range to reduce the likelihood of incorrect diagnoses resulting from measurement error and borderline results. The limits of the normal. inconclusive, and nonnormal ranges are based on three considerations: (1) the probability of misdiagnoses, (2) the expected frequency of inconclusive diagnoses, and (3) the reproducibility of the test results.

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Diagnoses based on quantitative laboratory tests may be inaccurate when the distributions of test results from "normal" and "nonnormal" individuals overlap. Ideally, the cutoff level used to distinguish normal from nonnormal test results is chosen to balance in some way the risk of false-positive diagnoses with the risk of false-negative diagnoses. However, a diagnosis cannot be made with absolute certainty; only an estimate of the probability of the diagnosis can be made. If the diagnostic criterion (laboratory cutoff level) used is established arbitrarily and without sta-

tistical validation, the diagnosis will be made with undefined or unwarranted confidence.

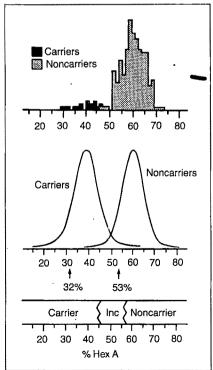
In this report, we present a method for evaluating the degree of overlap between normal and nonnormal results and quantifying the risks of misdiagnosis. Although the method proposed is widely applicable, we examine the problem of laboratory testing to screen for Tay-Sachs disease (TSD) carriers to illustrate our approach.

Tay-Sachs disease results from deficiency of the enzyme hexosaminidase A (Hex A), which is easily measured in serum. The activity of Hex A is usually expressed as a percentage of the total hexosaminidase activity (% Hex A). Although heterozygotes as a group typically have approximately 50% of normal enzyme activity, the distribution of their test results overlaps the distribution of noncarrier results (see Fig 1, which is the basis for all the examples in this report). There is, therefore, a finite probability that an individual with a test result in the "noncarrier range" is, in fact, a carrier, ie, there is a chance of misdiagnosis because a test result that appears to belong to one distribution really belongs to the other. Examination of raw data (Fig 1, top) may not be helpful and can even be misleading: although the carrier and noncarrier distributions clearly overlap at % Hex A of 46%, the extent of the overlap is not apparent, and a level of 53% appears to be unequivocally in the noncarrier range. However, examination of the theoretical distributions of % Hex A in the populations of carriers and noncarriers (Fig 1, bottom) reveals that a level of 53% is in the region of overlap. From these distributions, we can demonstrate that 93.3% of noncarriers are expected to have test results greater than

53%, while only 0.7% of carriers will have test results this high. (For the purpose of this illustration we will assume the data are normally distributed; how the population distributions are constructed will be described below.)

If we diagnose someone with a level of 53% as a noncarrier, it is critical that we know the probability of being wrong (ie, the probability of misclassification).

Fig 1.—Frequency distributions of percentage of total hexosaminidase activity (% Hex A). Top, Frequency histogram of sample data from 17 obligate heterozygotes (mean % Hex A = 39.0, SD = 4.8) and 501 noncarriers (mean % Hex A = 60.0, SD = 4.7). Bottom,Theoretical distributions of test results in the populations of carriers and noncarriers (assuming normality), based on the sample data shown in Fig 1, top. Inc indicates inconclusive range.



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This probability is a function not only of his or her test result, but of the frequency of carriers in the population as well. and can be estimated by applying Bayes' theorem. If we classify someone with a test result of 53% as a noncarrier and assume that his "prior" probability of being a carrier is .5 (a very bad assumption, since half the population is not heterozygous for the TSD gene), the estimated risk of misdiagnosis is 1 in 134. If the prior probability of being a carrier is .033 (eg, he is an Ashkenazi Jew), the estimated risk of misdiagnosis is 1 in 4000; if the prior probability is .003 (eg, he is not Jewish), the risk of misdiagnosis is only 1 in 45 000!

The application of Bayes' theorem to probability density functions for genotype assignment has been developed and elegantly presented by Gold1 and Gold et al² and reviewed by Murphy and Chase.8 This approach has been used to calculate the probability of heterozygosity for the TSD gene based on an individual's a priori risk and test result.1,2,4 Gold1 pointed out that both patients and referring physicians are interested in a diagnosis, not a probability of heterozygosity, and suggested that individuals with probabilities of heterozygosity greater than a prespecified critical probability be diagnosed as carriers. However, the choice of this critical probability is somewhat arbitrary and based on assumptions about the relative "costs" of misclassifying carriers and noncarriers. Furthermore, Gold's use of the standard Gaussian density function for the calculations, in which the population parameters (ie. mean and SD) are estimated, may not be appropriate when the reference samples are small.

The problem of defining a cutoff level is compounded by the irreproducibility inherent in any test procedure; despite all efforts to minimize between-assay variation, repeated assay of the same sample rarely yields precisely the same result. It is inevitable, therefore, that some individuals with borderline results will "cross the border" when the sample is reanalyzed, that is, they will have results in both the carrier and non-carrier ranges in repeated tests. How are these people to be counseled?

One solution to these problems has been to classify results in the region of

overlap as inconclusive⁵⁻⁷ (Fig 1, bottom). It is clear that by classifying a test result as inconclusive there is no risk of incorrect genotype assignment. However, the problem has merely been restated: how do we determine the limits of the inconclusive range? As the width of the inconclusive range is increased, the frequency of inconclusive diagnoses increases, and the usefulness of the test is diminished. On the other hand, as the width of the inconclusive range is decreased, the risk of making the wrong diagnosis (false-negative or false-positive) increases.

METHODS

We propose a systematic method for defining the limits of the inconclusive range (or indifference region) in such a way that the diagnostic implications of the specified inconclusive range are known. Specifically, for any inconclusive range, we want to know (1) the risk of incorrectly diagnosing an individual with a given test result, (2) the frequency of inconclusive diagnoses, and (3) the probability of a borderline sample having a result in the carrier range on one occasion and in the noncarrier range on another.

Our method details the calculation of these three probabilities so that the diagnostic consequences of different inconclusive ranges can be evaluated. First, because the entire population of nonnormals and normals cannot be tested, sample data must be collected and used to estimate the parameters (ie, mean and SD) of the population distributions for normals and nonnormals. Second, these statistics are used to determine the expected frequencies of nonnormal, inconclusive, and normal diagnoses for any given inconclusive range. Third, the risks of misclassification are derived. These probabilities are then used to evaluate the limits of the inconclusive range in light of the reproducibility of the test procedure itself.

Assumptions

The technique and conditions used for the measurement of % *Hex A* are obviously paramount and have been reviewed in detail. Two additional assumptions require emphasis: (1) the normative data must be derived in the laboratory where they are to be used, since subtle differences in technique and intangible variables may introduce a systematic bias in the results; and (2) the test result of a single individual may be included only once in the data set, even if multiple determinations have been made on a single sample or on several samples from the same person.

Throughout this discussion, we assume that the test results are normally distributed within the populations of carriers and noncarriers. In some testing situations, this assumption may be inappropriate, and log transformation of the data may result in a more normal distribution. In other circumstances, a simple transformation of the data may not be appropriate, and a non-Gaussian model would be needed. However, a discussion of modeling non-Gaussian sample distributions is beyond the scope of this article.

Characterizing the Carrier and Noncarrier Distributions

Ideally, the two distributions are defined by using test results from individuals whose diagnosis is known with a priori certainty. In the case of TSD, the reference carrier distribution is defined by testing obligate heterozygotes (ie, individuals who have either had a child with TSD or a pregnancy in which the fetus proved to be affected). (Data from carriers ascertained through screening may introduce a bias in the data, since heterozygotes with lower levels of % Hex A are more likely to be recognized as carriers than are those with higher levels.) On the other hand, reference noncarrier controls cannot be identified as confidently, since their heterozygosity can only be excluded by the test procedure itself. Data derived from non-Jewish individuals, who are significantly less likely to be heterozygous, may be used to minimize this ascertainment bias. The mean and SD of the carrier and noncarrier samples are calculated and serve as estimates of the parameters ofthe population distributions.

If we could determine the population parameters (mean and variance), the standard normal distribution (z-distribution) could be used to compute probabilities. However, the sample of people screened in most laboratories is relatively small. For this reason, the sample mean and variance may not be treated

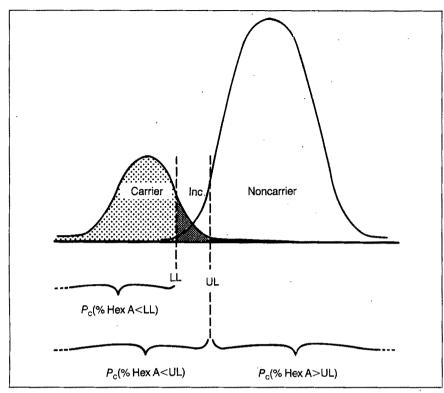


Fig 2.—Theoretical frequency distributions of percentage of total hexosaminidase activity that is hexosaminidase A (% *Hex A*) (abscissa) in carriers and noncarriers. *LL* and *UL* are lower and upper limits of inconclusive range (Inc), respectively. See text for details.

as if they were the population mean and variance, and use of the z-distribution is inappropriate, even though the levels of % Hex A (and many other clinical measures) are assumed to be normally distributed. In many cases, the t-distribution can be used (eg, in some tests of statistical significance), but our particular application requires the use of a related distribution, the noncentral t-distribution, which is used in the evaluation of statistical power and actually includes the usual t-distribution as a special case.

Estimating the Frequencies of Definitive Diagnoses for a Given Inconclusive Range

The expected frequencies of the various diagnoses can be determined from the theoretical distributions of nonnormal (carrier) and normal (noncarrier) test results in the population. Figure 2 illustrates these distributions, with the inconclusive range arbitrarily defined to have a lower limit (LL) and upper limit (UL). The probability of a carrier having a % Hex A within the carrier

range, P_c {% $Hex\ A < LL$ }, is represented by the fraction of the carrier distribution to the left of LL (lightly shaded area). The probability of a carrier having a test result in the noncarrier range. P_{c} {% Hex A>UL}, is represented by the fraction of the carrier distribution to the right of UL (blackened area). The probability of a carrier having a test result in the inconclusive range is represented by the fraction of the carrier distribution to the left of UL and to the right of LL (darkly shaded area). This is equal to the probability of a carrier having a % Hex A less than UL (ie, P_c {% $Hex\ A < UL$) minus the probability of having a % Hex A less than LL (ie, P_c {% Hex A < LL).

These probabilities may be found using the noncentral *t*-distribution (see "The Noncentral *t*-Distribution").

By using this method, one may determine the frequency of the three classifications for the population of carriers and noncarriers for any arbitrarily defined inconclusive range. Using the sample data set of % *Hex A* in serum, the effect of shifting the inconclusive range is shown in Table 1.

Table 1.—Effect of Choice of Inconclusive Range on Frequency of Inconclusive and Incorrect Classifications

	Inconclusive Range, %			
	44-49	46-51	48-53	
Carriers classified, Correctly	% 83.2	90.8	95.4	
As inconclusive	13.6	7.7	3.9	
Incorrectly	3.2	1.5	0.7	
Noncarriers classified, % Correctly 99.05 97.3 93.3				
As inconclusive	0.92	2.6	6.2	
Incorrectly	0.03	0.1	0.5	

Estimating the Risks of Misclassification

The numerical risk of misclassification is determined by the frequency of nonnormals in the population as well as the individual's test result. It has been determined empirically that an Ashkenazi Jew has approximately a 1 in 30 chance of being heterozygous for the TSD gene. 9,10 Therefore, calculation of the actual (posterior) probability of misclassification must also consider this prior probability of being heterozygous in addition to the "conditional" probability based on testing. This is readily accomplished through application of Bayes' theorem, which is shown in Table 2.

The derivations of the conditional probabilities are illustrated in Fig 3.4f an individual's test result is in the carrier range, $P_{\rm c}$ represents the probability of a carrier having a test result at or below the observed value (Fig 3, top left). The value of P_c may be obtained from formula 2 (see "The Noncentral t-Distribution"), substituting Obs % Hex A for UL. P_{NC} represents the probability of a noncarrier having a test result this low or lower (Fig 3, bottom left). The value of P_{NC} is also found from formula 2, substituting Obs % Hex A for UL and using the noncarrier mean and SD instead of \bar{X}_c and s_c . The joint probabilities are obtained by multiplying the prior and conditional probabilities. Since the sum of the posterior probabilities must equal one, the joint probabilities are "normed" using the sum of the joint probabilities as the common denominator. It is then seen that the sum of the posterior probabilities does equal unity. The derivation of the conditional probabilities when an individual's test result is in the noncarrier range is illustrated in Fig 3, top right and bottom right. Table 3 illustrates the probabilities of misclassification derived from the same data set used in Table 1.

The posterior probability is the probability (over many replications with different people) of correct genotype assignment at a given test result. From the perspective of establishing a diagnostic criterion, the critical data are the risks of misclassifying individuals of known genotype. An individual's genotype is determined long before he or she seeks testing. It is our ability to determine correctly the genotype of individuals in the population that must be evaluated.

Evaluating the Limits of the Inconclusive Range

The criteria used for genotype assignment should be sufficiently conservative to minimize the risk of labeling a carrier as a noncarrier (ie, false negative). However, as the criterion for excluding heterozygosity becomes more conservative, the frequency of false positives and inconclusive results increases. Therefore, the selection of the upper and lower limits of the inconclusive range should be based in part on the expected frequencies of inconclusive and incorrect diagnoses and the associated risks of misclassification.

There are several possible methods for selecting the inconclusive range. One method is to choose "acceptable" probabilities of misclassification and then find the corresponding levels of % Hex A. A second method is to impose a formal "loss function" that weighs the "cost" of each diagnosis (whether correct, incorrect, or inconclusive) by the probability of its occurrence. The inconclusive range is then chosen to minimize the overall loss. This assumes that we can define the costs of all possible diagnoses in all possible situations. We prefer a more heuristic approach, which does not assume the knowledge of such costs, and which considers the frequency of inconclusive diagnoses as well as the risks of misclassification. In addition, the reproductibility of the test pro-

	Genotype		
Probability	Noncarrier	Carrier	
Prior	29/30	1/30	
Conditional (based on testing)	P _{NC}	Pc	
Joint	(29/30)(P _{NC})	(1/30)(P _c)	
Posterior	(29/30)(P _{NO})	$(1/30)(P_c)$	
	$(29/30)(P_{NC}) + (1/30)(P_{C})$	$(29/30)(P_{NC}) + (1/30)(P_{CC})$	

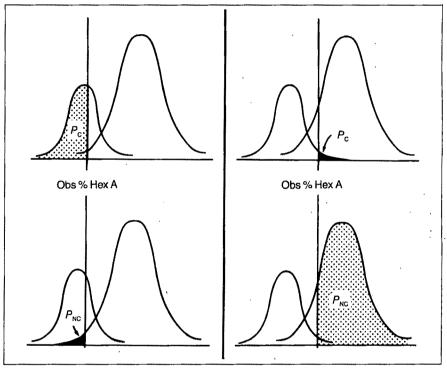


Fig 3.—Derivation of conditional probabilities of correct genotype assignment. Left, When test result is in the carrier range: top, for carriers; bottom, for noncarriers. Right, When test result is in the noncarrier range: top, for carriers; bottom, for noncarriers. See text for details. *Obs* % *Hex A* indicates observed percentage of total hexosaminidase activity that is hexosaminidase A.

Table 3.—Probability of Correct Genotype Assignment When Prior Probability of
Heterozygosity Is .033*

If Diagnosed as Carrier		If Dia	carrier		
% Hex A	Correct	Incorrect	% Hex A	Correct	Incorrect
38	.99991	.00009	49	.99890	.00110
40	.99940	.00060	51	.99948	.00052
42	.99720	.00280	, 53	.99975	.00025
44	.98804	.01196	55	.99988	.00012
46	.95495	.04505	57	.99994	.00006
48	.85972	.14028	59	.99999	.00001

^{*%} Hex A indicates the percentage of total hexosaminidase activity that is hexosaminidase A.

cedure (ie, precision) must also be taken into account.

Because no laboratory measurement is perfectly reproducible, repeated assay of the same sample will give a range of results. It is often desirable to have the inconclusive range be greater than the usual range of measurement error so that a given sample will not likely yield a result in the carrier range on one occasion and in the noncarrier range when tested again on a different day. Since it is between-assay variation with which we are concerned, we propose using the SD obtained from repeated assay of the same sample on different days as an index of measurement error. If repeated assays are performed on several samples, the SD derived from the weighted mean of the variance for each sample is used and is found from formula 1, which follows:

$$(1)\sqrt{\frac{\sum\limits_{\sum (s_i^2)(n_i-1)}^K}{\sum\limits_{N-K}}}, \quad \text{where } N = \sum\limits_{i=1}^K n_i$$

where K is the number of samples, n_i the number of measurements on a given sample, and s_i the SD of measurements from a given sample.

A specimen with a mean test result in the middle of the inconclusive range has the highest probability of having individual test results that are above the limit of the inconclusive range on one occasion and below the limit on another occasion (assuming that the conditional distribution of test results is symmetric). We suggest that if the inconclusive range is approximately four times the between-assay SD (ie, ± 2 SDs), the probability of this occurring will be acceptably low. The actual probability may be found as before, by substituting the median level of the inconclusive range for \bar{X}_{c} and the between-assay SD for s_c in formula 2 (below). The noncentral t-distribution is again used, but this time the "two-tailed" probability is sought. In our sample data, the between-assay SD (based on repeated assay of % Hex A in serum, N = 105) is 1.4. If the inconclusive range is 5 (3.57 SD), a 92.1% confidence interval is established.

Considering the size of the inconclusive range, the population distribution of test results (Table 1), and the risks of misclassification (Table 3), the inconclusive range 46 to 51 permits conservative genotype assignments, while minimiz-

ing the frequency of inconclusive diagnoses.

The Computer Program

Although performing the calculations and obtaining the precise probabilities from a table of the standard normal distribution is quite tedious, these procedures were readily programmed for execution on a microcomputer. The appropriate probabilities are derived by the program using an algorithm for the integral of the Gaussian probability density function.

The Noncentral t-Distribution

The evaluation of probabilities that % $Hex\ A$ exceeds (or is smaller than) critical levels is accomplished using the noncentral t-distribution. Suppose that % $Hex\ A$ in the carrier population is normally distributed with a mean $\mu_{\rm C}$ and variance $\sigma_{\rm C}^{\ 2}$. Then

$$P_{c}$$
{% $Hex\ A < X_{o}$ } = P_{c} { $T = (\%\ Hex\ A - X_{o})/s_{c} < 0$ },

where X_{a} is a prespecified constant and s_c is the sample SD of the known carrier population. It follows that the statistic T has the noncentral t-distribution with (n-1) degrees of freedom and noncenparameter $\lambda = (\mu_c - X_o)/\sigma_c$, where n is the size of the sample of known carriers. We estimate \(\lambda \) by $\hat{\lambda} = (c)(X_{\rm C} - X_{\rm o})/s_{\rm C},$ using c=1-[3/(4n-5)], which is an (almost) unbiased estimator of \(\lambda \). 12 We evaluate $P_{c}\{T<0\}$ by using the Johnson-Welch¹⁸ approximation to the noncentral t-distribution, namely that T is distributed approximately as $N(\lambda, 1 + \lambda^2/2)$.

We use the standard normal distribution to approximate the noncentral t-distribution. ¹⁸ For example, P_c {% $Hex\ A>UL$ } (Fig 2) is found by calculating the probability of a z score less than

(2)
$$z = \frac{(UL - \bar{X}_{c})(c)}{s_{c} \sqrt{1 + \frac{(UL - \bar{X}_{c})^{2}(c^{2})}{2s_{c}^{2}(n-1)}}}$$

where c=1-[3/(4n-5)] (formula 2). This probability can then be found in any table of the standard normal (z-) distribution.

COMMENT

Laboratory test results are a major component of the diagnostic armamentarium, both for diagnosis of existing disease and identification of those at risk for developing disease (ie, for screening). Individuals found to be "at risk" often take measures to reduce the likelihood of disease. In the specific example we have used, couples found to be TSD ∃arriers can undergo prenatal diagnosis and selective abortion. This approach has led to a reduction of the incidenc∈ of TSD.¹⁴ Unfortunately, little has been published in the general medical literature on statistically meaningful and clinically useful methods for identifying those at risk.¹³,16-17

The method we describe permits the definition and evaluation of meaningful diagnostic criteria based on relatively small samples, which may not precisely reflect the parameters of the normal distribution. The diagnostic criteria used are established after consideration of three factors: (1) the Bayesian probabilities of misdiagnosis, (2) the frequency of incorrect and inconclusive diagnoses in the population of normals and nonnormals (e.g., carriers and noncarriers), and (3) the reproducibility of the laboratory assay.

By employing an inconclusive range. we are able to minimize the risks and anxieties caused by unavoidable between-assay variation and borderline results, problems that, to our knowledge, have not been previously addressed. Consequently, individuals with conclusive results may be counseled with greater confidence. The frequency of incorrect diagnoses is considerably reduced (Table 1) and the risk of an individual being misclassified is also greatly diminished (Table 3). The inconclusiv∈ range also reduces the anxiety created by borderline test results. Because the laboratory assay is not perfectly precise, it is entirely appropriate that some individuals (those with borderline results) remain undiagnosed. If the inconclusive range is approximately four times the range of variability of the assay, the danger of misclassification based solely on technical variation is substantially reduced. If individuals with inconclusive test results assume they are carriers, they are, in effect, assuming the burden of the enhanced confidence from which the rest of the screened population benefits. If we assume that the belief that one is a carrier for the TSD gene puts one at certain risks (eg, amniocentesis), this method partitions these risks within the population in a predictable and well-defined manner. We feel this is preferable to accepting a higher false-negative rate.

Our method may be used to establish cutoff levels for any test that is used to discriminate two groups of subjects. It

is particularly suited to screening programs where the prior probabilities or incidences of the diseases are known (eg, newborn screening for phenylketonuria based on the blood phenylalanine level, screening for congenital hypothyroidism based on the level of thyroxine, maternal serum alpha-fetoprotein screening during pregnancy for the detection of open neural tube defects). Even when the prior probability is not known and is assumed to equal .5, the use of an inconclusive range and the noncentral t-distribution may still be quite appropriate. For example, our method could be applied to establishing a cutoff level for distinguishing euthyroid from hypothyroid individuals based on the level of free thyroxine, or determining the risk of neonatal sepsis based on the absolute neutrophil count. The only prerequisites are that reference data can be obtained from individuals whose diagnosis has been established by some means other than the screening test itself (eg, thyroid-stimulating hormone and thyroid scan, blood culture), and the test results are normally distributed.

This discussion is limited to situations in which only one test (ie, conditional probability) is utilized for reaching a diagnosis. There are certainly many instances when more than one test result will contribute to a diagnosis. Our approach can be generalized to more complex situations, but a detailed discussion of this is beyond the scope of the

present study.

Although an unequivocal diagnosis is the goal of laboratory testing, such certainty is rarely attainable. Nonetheless, it is often possible to define precisely the limits of the test procedure and the risks of misdiagnosis. The model we have described is useful in the laboratory for the definition of meaningful diagnostic criteria for a variety of test procedures. These diagnostic criteria reflect the reproducibility of the test procedure and the discriminatory power of the test, and directly express the certainty of the diagnosis.

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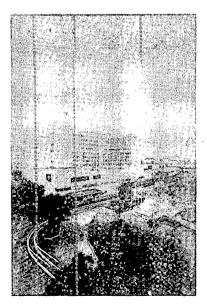
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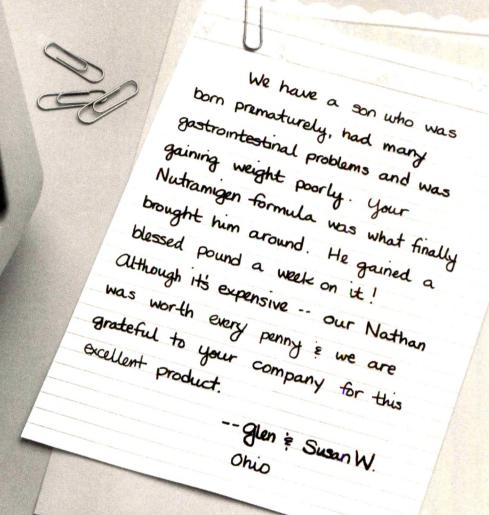
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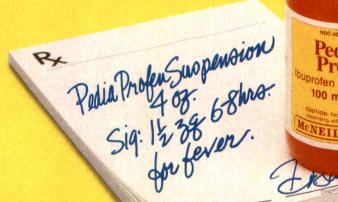
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A new alternative for fever Pedia Profen

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The following is a brief summary only. Before prescribing, see complete prescribing information in **PediaProfen** labeling.

INDICATIONS AND USAGE: PediaProfen is indicated for the reduction of fever in patients aged 6 onths and older, and for the relief of mild-to-moderate pain in patients aged 12 years and older.

CLINICAL PHARMACOLOGY: Controlled clinical trials comparing doses of 5 and 10 mg/kg ibuprofen

and 10-15 mg/kg of acetaminophen have been conducted in children 6 months to 12 years of age with fever primarily due to viral illnesses. In these studies there were no differences between treatments in fever reduction for the first hour and maximum fever reduction occurred between 2 and 4 hours. Response after 1 hour was dependent on both the level of temperature elevation as well as the treatment. In children with baseline temperatures at or below 102.5°F, both ibuprofen doses and acetaminophen were equally effective in their maximum effect. In those children with temperatures above 102.5°F, the ibuprofen 10 mg/kg dose was more effective. By 6 hours children treated with ibuprofen 5 mg/kg tended to have recurrence of fever, whereas children treated with ibuprofen 10 mg/ kg still had significant fever reduction at 8 hours. In control groups treated with 10 mg/kg ace-taminophen, fever reduction resembled that seen in children treated with 5 mg/kg of ibuprofen, with the exception that temperature elevation tended to return 1-2 hours earlier.

CONTRAINDICATIONS: Pedia Profen should not be used in patients who have previously exhibited

hypersensitivity to ibuprofen, or in individuals with all or part of the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents. Anaphylactoid reactions have occurred in such patients.

WARNINGS: Risk of GI Ulceration, Bleeding and Perforation with NSAID Therapy. Serious gastro-intestinal toxicity such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAID therapy. Although minor upper gastro-intestinal problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs even in the absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approx-imately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulcerasex) have been associated with incleased in Section to be detailed by the content of the content are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

PRECAUTIONS: General: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints while receiving PediaProfen, the drug should be discontinued and the patient should have an ophthalmologic examination which includes central visual fields and color vision testing.

Fluid retention and edema have been reported in association with ibuprofen; therefore, the drug

should be used with caution in patients with a history of cardiac decompensation or hypertension.

PediaProfen, like other nonsteroidal anti-inflammatory agents, can inhibit platelet aggregation, but the effect is quantitatively less and of shorter duration than that seen with aspirin. Ibuprofen has been shown to prolong bleeding time (but within the normal range) in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying hemostatic defects, PediaProfen should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy

Patients on **PediaProfen** should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

In order to avoid exacerbation of disease of adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ibuprofen is added to the treatment program.

The antipyretic and anti-inflammatory activity of **PediaProfen** may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Since ibuprofen is eliminated primarily by the kidney, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation. Prospective studies on the safety of ibuprofen in patients with chronic renal failure have

Safety and efficacy of PediaProfen in children below the age of 6 months has not been established.

Pregnancy: Reproductive studies conducted in rats and rabbits at doses somewhat less than the maximal clinical dose did not demonstrate evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. As there are no adequate and well-controlled studies in pregnant women, this drug should be used during pregnancy only if clearly needed. Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovascular system (closure of ductus arteriosus), use during late pregnancy should be avoided. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed occurred in rats. Administration of Pedia Profen is not recommended during pregnancy.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with ibuprofen is gastrointestinal. In controlled clinical trials, the percentage of adult patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

Adverse reactions occurring in 3% to 9% of patients treated with ibuprofen: nausea, epigastric Adverse reactions occurring in 5% to 5% or patients treated with louprotein naises, epigastric pain, hearthurn, dizziness, rash. Adverse reactions occurring in 1% to 3% of patients: diarrhea, abdominal distress, naisea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract, headache, nervousness, pruritus, tinnitus, decreased appetite, edema, fluid retention (generally responds promptly to drug discontinuation). Still other reactions (less than 1 in 100) have been reported, and are detailed in the full summary of prescribing information.

DOSAGE AND ADMINISTRATION: Shake well prior to administration.

Fever Reduction in Children 6 months to 12 years of age: Dosage should be adjusted on the basis of the initial temperature level (See CLINICAL PHARMACOLOGY for a description of the controlled clinical trial results). The recommended dose is 5 mg/kg if the baseline temperature is less that 102.5 °F or 10 mg/kg if the baseline temperature is greater than 102.5 °F. The duration of fever reduction is generally 6-8 hours and is longer with the higher dose. The recommended maximum daily dose is

Mild to moderate pain: 400 mg every 4 to 6 hours as necessary for the relief of pain in adults In controlled analgesic clinical trials, doses of ibuprofen greater than 400 mg were no more effective than 400 mg dose

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The Pediatric Forum

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Dialogues With Henry

July 1989

I dreamed that I died last night. It wasn't a pleasant feeling. I was floating in the air above my body. It was lying in a coffin. It was peaceful for a few seconds, lying there. But then I realized what was happening. I woke up and couldn't go back to sleep.

I've dreamed about dying before, but never like this. Like I'd be in a big battle, shooting down the enemy with a machine gun . . . and then being shot. But this dream was different.

I can't believe this is happening to me. It doesn't seem real. I feel like I'm in a haze. If you told me 2 weeks ago that I would be this sick, this soon, I'd have said you're crazy. I mean, here I am, talking about dying.

Every friggin' day is worse. Every day when I don't get better is like another nail being driven into my cof-

I feel so weak. I don't even feel like getting up to take a dump. Can you believe it? Something natural like that? Shit. I don't even want to do that. I feel dizzy when I get up. Really woozy, like I'm very drunk.

I hate waking up in the morning and feeling choked. Sometimes I don't want to wake up.

I had no idea it would be this bad. I thought I'd be sick for a week or two and that would be it. When I came in for cleanouts I thought, geez, this is really bad—I have to miss school—I miss my friends. But I didn't know how bad it could be.

This really sucks.

When we talked 3 years ago, all I was worried about was who I was going to take to the freshman prom. How easy that was.

I'm not even coughing well anymore. It used to be so easy. I would come in for a cleanout and then in a few days I would be back on my feet. No big deal. I guess things get harder when you get older.

I'm glad I lived 20 years. I wouldn't do anything differently. I had a good life, good friends. Maybe tonight I'll write little notes to my parents and friends. You know, personal notes. If I feel up to it.

I don't think I'm going to make it out through the front doors of the damn hospital. It's like a little voice inside me, telling me that. It's not that I've given up hope. It's just this little voice. You know what I mean?

June 1989

Am I going to make it?

I don't know. What you've got to try to do today is to receive as much chest physiotherapy as possible. You're getting antibiotics and other drugs to help you breathe.

There is an old proverb: Parting is a little death. It's so true.

I want you to know that our relationship will spur me to find a treatment for this disease.

I'm glad. I hope you find it. Even if it's too late for me.

You won't be forgotten.
That's what people tell me.

March 1986

What bothers me most about my disease is that I can't keep up with my friends. Like when we're walking I have to slow down after a while and they have to slow down and walk with me.

I used to pretend that I wasn't sick and would give my mother a hard time. But now I've accepted my illness. I make sure to do my physical therapy every day because it's for my own good. I guess I've grown up.

I sometimes think about dying. I wonder how it's going to happen. Am I going to be driving a car and just drop dead? Or am I going to get really sick one day? When a friend of mine died last year it really put me off the track for a week. But it doesn't bother me all the time. When I talk with other sick kids we never talk about it. We all know what it's about.

If I met a 10-year-old kid with my disease, I wouldn't want to tell him anything in particular. I wouldn't want to scare him.

If it weren't for my illness I would want to be an airplane pilot. But right now I want to be a phlebotomist . . . after I finish high school.

I want to get married. I would marry someone who would understand me and my disease. I would never have kids because I wouldn't want them to go through what I've gone through, and I wouldn't want to go through it as a parent. I suppose it would have been better if I hadn't been born. It would have been easier on my parents and me.

But I've never felt like calling it quits. Sometimes, when I see another kid throw their life away—like doing drugs—and they'll probably die in an accident, I wish that they had my disease instead of me.

I don't want to be a burden on my parents. It's hard for them to come to the hospital every day. I don't even like the ride here every 3 months. They never had any children after me. My parents were divorced the same year that my disease was diagnosed. They've both remarried but still don't have other kids.

August 1983

Look at that fountain with all those coins!

Do you know why there are pennies in there?

Sure. People make wishes there. You know what I would wish for if I had one wish?

Something serious?

Something serious.

Tell me.

I would wish for a cure for cystic fibrosis.

I hear you.

Can I have a penny?

This article is based on interviews conducted at Massachusetts General Hospital, Boston.

RAN D. ANBAR, MD Division of Pulmonary Medicine Department of Pediatrics Children's Hospital of Philadelphia 34th Street and

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Stress in Residency

Sir.—In the February 1989 issue of AJDC, Dr Hoekelman¹ discussed sources of stress in pediatric residency and suggested possible ways in which

it can be reduced. Dr Hoekelman listed eight sources of stress that included learning to be a physician, having a family, having relatively low income, and being in a highly competitive environment. Dr Hoekelman suggested that reduction of stress would occur if each resident had an advisor, if 4 weeks' vacation were given each year, and if consecutive hours of work numbered no more than 29. He also suggested that a reduced schedule option be available, that maternity and paternity leaves be granted, and that residents organize and participate in social events with the faculty.

I am a practicing pediatrician in a group of seven pediatricians, and I found this article disturbing. I have always considered residency to be a preparation for the practice of pediatrics. If my experience in practice is representative, pediatric practice is inherently stressful. Each member of our group works 50 hours per week of patient time, and, if overnight call is included, 60 hours per week. Since we attend all cesarean sections, and a disproportionate number of them seem to occur between midnight and 6 AM, I believe that the members of our group would include the overnight hours in calculating our work schedule. We also answer an average of six or seven telephone calls after our office closes at 10 PM and take care of any emergency that comes into our emergency department during the night.

This schedule is more stressful than my colleagues and I would like at times. Coming into the office the next day after being up all or part of a night can be very difficult. However, we follow this system primarily because, in our opinion, it provides continuity and the best quality of care to the children we treat. If we were to evaluate and treat a child with meningitis at midnight and then tell the parents that another physician would take over in the morning because our shift was over, the patient would be ill served. in my opinion.

In other words, pediatric residencies need to be stressful precisely because private practice is stressful. Furthermore, the question needs to be "What is best for the patient?" not "What is easiest for the physician?"

The number of people going into the full-time practice of pediatrics seems to be declining. There could be many reasons for this decline. Perhaps they are being taught to avoid stress, that they will not be able to handle stress. and that they should choose a career that is "easier." The sources of stress listed in the first paragraph have not changed since the early 1960s when I began medical school and are unlikely to change. It is tough becoming a physician. It should be tough.

Would the result of changes recommended by Dr Hoekelman not change the entire way pediatrics is now practiced? Do we really want to create a bunch of "9-to-5" physicians? Has evervone given enough thought to how the patient is best served? If this article reflects the thinking of others in academic medicine, the issue should be carefully reexamined.

Unless and until we find a way to practice caring and quality pediatrics without stress, our pediatric residency programs need, properly, to be stressful and indeed to train the physicians to cope with stress rather than avoid stress.

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In Reply. - One might think after reading Dr Benjamin's letter that he and I are at opposite ends of the pole on the issue of reducing stress in residency training. Actually, we are

Dr Benjamin and his six partners put in, on average, a 60-hour workweek and go to work on days after they have been up taking care of patients for part or all of the preceding night. They have a stressful schedule, working 20 hours a week more than most people. Dr Benjamin feels that residency training programs should be stressful to prepare physicians to cope with the stress they will face when they enter practice.

The question is, how stressful does a residency need to be to teach young physicians how to cope with stress? Do they need to work more than 80 hours a week (as Dr Benjamin did when he was a resident) to prepare them for a 60-hour workweek in practice? New York State Department of Health regulations in effect since July 1989 limit the number of consecutive hours a resident can work in direct patient-care activities to 24 and the number of hours worked per week to 80, when averaged over a 4-week period. That is far more than Dr Benjamin and his colleagues work. Young physicians fresh out of training who are recruited to Dr Benjamin's practice will consider their new schedule much less stressful than the one they had the previous 3 years, and they will be prepared to cope with it.

Dr Benjamin asks that, in designing residency schedules, we consider what is best for the patient rather than what is easiest for the physician. I don't think the two positions can be separated. Exhausted physicians render poor patient care. While continuity of care is desirable over time, discontinuity of care (transferring responsibility of care from one physician to another) in acute illness situations has never been proved to be bad for patients. Indeed, it makes sense to have a well-rested physician take over, particularly if the patient has a critical illness that requires the application of complicated diagnostic and therapeutic procedures.

As pediatricians, we apply the concepts of health promotion and disease prevention. Training program directors need to apply these same concepts when designing pediatric residents' work schedules.² Directors have a responsibility-a very heavy one-to bring their trainees to a high degree of clinical competence in a way that does not interfere with a reasonably balanced life-style for the residents both during and after training, and in so doing, avoid the poor interpersonal functioning and impairment of professional performance that afflict so many physicians.3

Finally, I would like to reassure Dr Benjamin that the number of people entering the full-time practice of pediatrics is not declining. There has been a steady growth in the number of office-based pediatricians in the United States from 1964 projected through 19904; between 1988 and 1990 that number was expected to grow from 27855 to 31597. Equally important, the percentage of office-based pediatricians vs total pediatricians, which was 63.9% in 1980, will rise to 67.5% in 1990.

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Management of Croup

Sir. - We read with interest the article in the September 1989 issue of AJDC by Skolnik.1 This article purports "to critically review and synthesize the complete body of English-language literature on the medical treatment of croup and formulate a set of recommendations to guide physicians in making treatment decisions for children with croup who require hospitalization." Unfortunately, the article is woefully lacking in terms of management decisions that must be made in some critically ill children with croup. From the outset, Dr Skolnik misrepresents the true nature of the disease entity. He defines croup as a syndrome of laryngeal obstruction when, in fact, it is generally recognized to be a diffuse inflammatory condition of the larynx, trachea, and bronchi. In many circles, the term laryngotracheobronchitis is much preferred to the term croup. In his review, Dr Skolnik tends to neglect the tracheal and bronchial involvement that many times complicate the management of this form of airway obstruction.

In the most severe cases of those children who require hospitalization, medical management will fail, and further intervention for airway support will be required.²⁻⁴ The issue of intubation is only superficially addressed and, unfortunately, one is left searching the bibliography to fill this gap.

While guidelines have not been established for conversion of intubation to tracheotomy in children with severe croup, the issue should at least be addressed in a review article of this nature. In addition, the use of endoscopy in the determination of when a tracheotomy might be necessary is not addressed. Endoscopy may similarly be important in the evaluation of those patients with recurrent croup in whom a subglottic stenosis may be present. Patients with atypical cases of croup may also benefit from an endoscopic procedure to determine whether there

is a coexistent cause of airway obstruction. In failing to address these important issues, Skolnik's review is incomplete and does not offer the clinician the benefit of a management perspective for those patients who are most severely affected with laryngotracheobronchitis.

In summary, the points that Skolnik addresses in his article are helpful for the clinician and well supported by his review of the literature. Unfortunately, his rather limited look at this disease process prevents the practitioner from exploring all potential management alternatives.

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4. Mitchell DP, Thomas RL. Secondary airway support in the management of croup. *J Otolaryngol.* 1980;9:419-422.

In Reply.—I want to thank Drs Myer and Holmes for illustrating an important point about critically reading the medical literature. The purpose of my article was, as stated in the introduction, to review the medical, not the surgical, treatment of croup. I chose to define the scope of the article in this way to address treatment concerns for 95% to 99% of children admitted to the hospital with croup. ¹⁻³ The medical treatment of croup has not been comprehensively reviewed in the recent literature.

A review of issues surrounding the topics of intubation, tracheotomy, and endoscopic evaluation, while important, has been done recently, 4.5 but doesn't come under the stated purpose of my article.

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Growth Velocity Values Measured During Short Observation Periods May Obscure Effects of Treatment of Growth Failure

Sir.—Growth velocity charts are often used to indicate changes in growth rates over short periods. Eager investigators have a special nurse make a number of measurements in children with growth failure, using a stadiometer every 2 to 3 months after treatment with a hormone, a vitamin, or a special diet, perhaps given by a feeding tube, has been initiated. These measurements are then extrapolated and used with growth velocity standards such as those published by Tanner and Davies.¹

The problem rests with the length of the interval between measurements. Let us assume that they are obtained every 3 months. Growth velocity data are published in centimeters per year. The investigator simply multiplies the result by 4. This also multiplies observer bias and measurement error by 4. Here is a hypothetical example. The measurements in the tabulation below were obtained during a year in which a child would grow a total of 6 cm and, therefore, the mean growth velocity for age indeed is 6 cm/y:

	Observed Growth,	Extrapolated Rate,	
Quarter	cm	cm/y	
1st	1.5	6.0	
2nd	1.0	4.0	
3rd	1.6	6.4	
4th	1.9	6.6	

This looks pretty good on a scattergram. Three values are normal or above, and the one small value, just 4 cm/y, does not seem to be very important. However, the originator of growth velocity standards, J. M. Tanner, MD, DSc, recommended that,

these charts refer to whole-year velocities converted from increments that should be taken over not less than 0.85 years and not more than 1.15 years. Velocities calculated over shorter periods reflect seasonal effects (most children grow faster in the spring and slower in the fall) and are

relatively more affected by the unavoidable errors in measurement (which should not exceed 3 mm).¹

My recommendation is simple. Let us use growth velocity curves for yearly measurements only, and also ask for z scores when we want to document the effect of certain treatments on the growth of individual children. The z score is the patient's height minus mean height for age divided by the SD of mean height for age.

In my view, real catch-up growth is proved only when z scores decrease. No one will argue that a treatment was effective if a child who was 3 SDs below the mean before treatment is found to be just 1 SD below the mean at the end of the observation period. While any method may have shortcomings, in all my studies of children with growth failure, I found it best to use z scores in the analysis of large amounts of growth data.

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1. Tanner JM, Davies PSW. Clinical longitudinal standards for height and height velocity for North American children. *J Pediatr.* 1985;107: 317-329.

In Reply.—The letter from Dr Stickler addresses two issues: (1) extrapolation of growth patterns from too short observation periods; and (2) use of z scores to document the growth observed in a child, as sequential measurements are examined. There is universal agreement among authorities in biometry that the data analyst should not draw inferences or make predictions outside the boundaries of the observed values. Growth observed for only a few months should not be used to estimate expected growth over a full year.

The use of z scores for evaluating growth status is less universally accepted. A z score is a concise way to express the distance of a particular value from the mean of a normally distributed set of values. A z score of "+1" is 1 SD above the mean; a z score of -1.5 is 1.5 SDs below the mean. This tidy notation has appeal because of its brevity, convenience, and wide applicability. But for many fastidious observers, z scores are fatally flawed.

The z score is an accurate index of

dispersion only if the values are distributed in normal (gaussian) form, which many growth measurements are not. Because growth values (such as weight) are often highly skewed, monographs and other reference documents may use percentiles rather than mean and SD to describe sets of body measurements.

This is more than mere pedantry. An example using data from the National Center for Health Statistics (NCHS)2 may help. A girl aged 7 years with weight at the fifth percentile for her age has a z score of -1.5. At 10 years of age, with weight still at the fifth percentile, her z score is -1.1. She was at the fifth percentile each time she was weighed. Relative to other girls of her age, she grew in a consistent weight channel. The change in her z score suggests that she had changed her growth track. The theory supporting z scores (normality) does not consistently accord with actual observation (skewness). The differences between theory (z scores) and empiric observation may be dismissed by some analysts as being "close enough." Nevertheless, the issue of normality should be discussed whenever z scores are used.

The growth data from NCHS² are presented in large tables and charts that employ seven percentile points. If means and SDs (*z* scores) were appropriate for describing growth data, their use in the NCHS publication would have greatly reduced its size and complexity. The observed growth data were not normally distributed, so NCHS was obliged to use percentiles.

In short, Dr Stickler's point about extrapolation of growth velocity from short observation periods is important; his assertions about *z* scores are less persuasive, in my opinion.

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High-Dose Intravenous Gamma Globulin Infusions in Hemolytic-Uremic Syndrome: A Preliminary Report

Sin.—The classic form of hemolyticuremic syndrome (HUS) follows a prodrome of bloody diarrhea due to verotoxin-producing Escherichia coli infection.1 Verotoxin damages endothelial cells2 and releases factor VIII. von Willebrand factor (vWF) antigen, and large multimers of vWF.3 These large vWF multimers, in the presence of a platelet agglutinating factor, may facilitate platelet aggregation, resulting in microthrombi and thrombocytopenia. A platelet agglutinating factor has been reported in HUS4 and can be inhibited by IgG obtained from adults only.4,5 Anecdotal reports suggest a beneficial effect of intravenous infusions of human gamma globulins (IVGG) in thrombotic thrombocytopenic purpura.6 Because the inciting factors and clinical manifestations of thrombotic thrombocytopenic purpura and HUS are similar, it is likely that both represent a spectrum of disease with a common mechanism7 and both might improve with IVGG therapy.

In our preliminary study, eight consecutively treated children (three boys, five girls; mean age, 3.75 years) with classic HUS and initial platelet counts of less than $100 \times 10^{\circ}$ /L received infusions of IVGG (Sandoglobulin), 400 mg/kg per day for 5 days. The severity of HUS, as classified by Gianantonio et al,8 was mild in three children, moderate in three children, and severe in two children.

The course of HUS in the children treated with IVGG infusions was compared with that in two historical groups of children with classic HUS previously seen by us. A group treated with fresh-frozen plasma (FFP) infusions was composed of 12 children-5 boys and 7 girls with a mean age of 4.75 years-with mild (6 children), moderate (4 children), or severe (2 children) HUS. A control group consisted of 23 children-8 boys and 15 girls with a mean age of 3 years—with mild (12 children), moderate (7 children), or severe (4 children) HUS who had received neither FFP nor IVGG (Table). These 35 children were from a group of 47 children with HUS treated from 1972 through 1985. Of the 12 children excluded, there were 9 whose initial platelet counts were 100 × 109/L or more, a criterion set to exclude IVGG therapy; 2 children were unavailable for follow-up; and 1 child had HUS associated with the onset of metastatic Wilms' tumor. The criteria for dialysis, such as anuria, volume overload, serum electrolyte abnormalities, and the severity of renal failure, were the same for all three groups. Packed red blood cells were transfused as required for a he-

matocrit value less than 0.20/L. The response to treatment was evaluated by (1) hematologic improvement by resolution of thrombocytopenia (rise in daily platelet count) and anemia (need for packed red blood cell transfusion to maintain a hematocrit value more than 0.20/L) and (2) renal function improvement by achievement of urine volume greater than 1 mL/kg per hour, reduction of serum creatinine less than 88 µmol/L, and the number of days that dialysis was required. The effect on long-term sequelae of HUS, such as hypertension, development of end-stage renal disease, and residual neurological abnormalities (ie, persistence of seizures requiring medications, abnormal electroencephalogram readings, persistent abnormalities on computed tomographic studies or radionuclide brain scans, and physical handicap) at the end of 2 years was compared. Deaths in each group were recorded. Severity of the HUS and male-to-female distribution in separate groups were evaluated by x2 analyses. Daily platelet counts were evaluated by Student's unpaired t test. Changes in platelet count during a period of 8 days in each of the three groups were analyzed9 to assess the trend in the increase of platelet counts. P<.05 was considered significant.

Treatment with IVGG was associated with statistically significant improvement in platelet counts in comparison with FFP treatment (P < .05)and controls (P < .01) (Figure) and the trend of increase in platelet counts in comparison with FFP treatment (P<.05) or no therapy (P<.001). Urine output increased significantly faster in the IVGG group compared with the control group (P < .05). Although the decrease in serum creatinine was faster with IVGG than FFP infusions when compared with the controls, it did not reach a statistically significant level. Transfusion and the length of dialysis requirements were not different. Long-term residua were absent with IVGG infusions (Table).

There were no adverse effects of IVGG or FFP infusions. Our preliminary data suggest that a total dose of 2 g/kg of IVGG infused over 5 days improved thrombocytopenia and shortened periods of oligoanuria and elevated serum creatinine in HUS. Both long-term morbidity and mortality also improved, suggesting possible therapeutic benefits. Additionally, the treatment was relatively safe.

The exact mode of action of IVGG

Effects of Intravenous Gamma Globulin (IVGG) Infusions on Resolution of Hemolytic-Uremic Syndrome (HUS)*

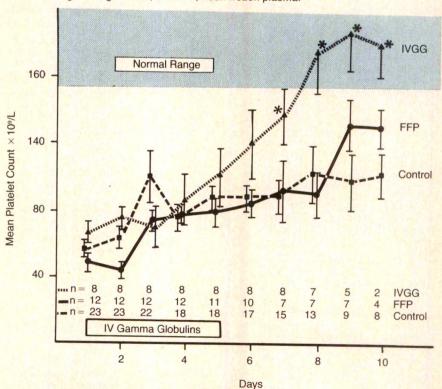
	IVGG (n=8)	FFP (n = 12)	Control (n = 23)
Age, y		4	25 01 (11 – 20)
Mean	3.75	4.25	3
(Range)	(2-9)	(0.5-9)	(0.5-9)
Sex, M/F	3/5	5/7	8/15
Severity of HUS,† mild/moderate/severe	3/3/2	6/4/2	12/7/4
Acute phase‡ Units of packed red blood cells transfused	5.6±1.0 (8)	5.0±1.1 (11)	4.0±0.7 (21)
No. of days for Urine volume, >1 mL/kg per h	5±1.0 (5)§	6.9±1.6 (7)	9.6±1.9 (14)
Serum creatinine,			(, ,)
<88 μmol/L	16 ± 4.3 (7)	34 ± 10.2 (10)	47.9 ± 20.9 (15)
Dialysis	7.6±0.9 (5)	6±1.2 (8)	7±1.1 (13)
Long-term sequelae			
Hypertension for >2 y	None	1/11	2/21
End-stage renal disease	None	1/11	2/21
Neurologic residua	None	5/11	5/21
Deaths	None	1/12	2/23

^{*}There were no significant differences between the groups as evaluated by Student's t test and χ^2 analysis. FFP indicates fresh-frozen plasma.

†Severity of HUS as described in text.8

||One-tailed P>.05.

Daily platelet count (mean \pm SEM) in patients with hemolytic-uremic syndrome. Numbers of patients decreased as those who reached a platelet count of greater than $150 \times 10^{\circ}/L$ were excluded. Boxed area labeled "IV Gamma Globulins" represents 5-day treatment in IVGG group only. Shaded area represents the normal range for platelet counts. Asterisk indicates statistically significant difference (P<.05) as evaluated by Student's t test; IVGG, intravenous gamma globulins; and FFP, fresh-frozen plasma.



[‡]Numbers in parentheses indicate assessable patients. Results expressed as mean \pm SEM. 8P < .05

in HUS remains unclear. Intravenous gamma globulin preparations, mostly obtained from pools of adult donors, have shown neutralizing activity against verotoxin in in vitro studies. 10 In 29 of 30 children without HUS, such neutralizing antibodies were absent and may predispose them to infection. 10 Hence, passive transfusion of this specific antibody in patients with HUS may possibly neutralize the verotoxin and shorten the course, and may explain the beneficial effects noted in our study. Alternatively, as suggested in idiopathic thrombocytopenic purpura, IVGG may block Fc receptors on platelets or reticuloendothelial cells and prevent platelet removal.11 A third possibility is that IVGG may inhibit the platelet agglutinating factor, as has been demonstrated in both in vitro3,4 and in vivo3 studies of patients with HUS and thrombocytopenic purpura. Because of the relative safety and possible therapeutic benefits of IVGG, we feel that a randomized controlled trial of IVGG in the early phase of HUS is warranted.

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Presented in part at the 19th Annual Meeting of the American Society of Nephrology, Washington, DC, December 9, 1986, and the 10th International Congress of Nephrology, London, England, July 27, 1987.

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Late Sudden Unexpected Deaths in **Hospitalized Infants With** Bronchopulmonary Dysplasia

Sir. - I am a home care physician and read with much concern the report of late sudden unexpected deaths in infants with bronchopulmonary dysplasia who required prolonged mechanical ventilation.1 During the past decade, I have been discharging patients and helping families manage their ventilator-assisted children at home.2 These children were medically stable, as defined by clinical course (no major diagnostic intervention or therapeutic changes within 1 month) and by clinical and physiologic criteria appropriate to age and underlying pathogenesis.3

Cases of patients with bronchopulmonary dysplasia who require home mechanical ventilation are represented in my experiences both in Illinois and in Pennsylvania.3,4 Such patients have required months of optimal ventilation as defined by patient eligibility criteria,4 and these cases have resulted in excellent outcomes for children who grow and develop and eventually become free of their need for oxygen and the ventilator.

Home mechanical ventilation is an outgrowth of home care for survivors of respiratory paralytic polio and other neuromuscular diseases.6 After an initial success, it has been applied to other, more difficult conditions, such as high spinal cord injury. Patients with cardiopulmonary conditions represent a greater set of challenges, with different prognoses, risks, and home care organizational and technological requirements.

Although there is a growing interest in home mechanical ventilation for patients with severe bronchopulmonary dysplasia, this option must only be chosen after we understand these differences. There is good reason to believe that abnormal function (ie, airway obstruction, low compliance, low functional residual capacity) exists well into the first year of life, and that it is best not to consider withdrawal of optimal ventilation until well into the second year of life.7 When these patients receive optimal ventilation (Pco₂ < 50 mm Hg, Pao₂ > 65 mm Hg, O₂ saturation >93%) they have greater functional reserve and do not exhibit intermittent cyanosis, fever, or other signs of medical instability.

Thus, candidates for home care must be medically managed by strict criteria, with great concern for medical stability. They should not be prematurely considered for home care for cost-containment purposes. Other options, such as specially designated transitional units, may be a cost-effective alternative. The observations by Abman et al1 make this recommendation all the more important.

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Attitudes Regarding Parental Presence During Medical Procedures

Sir.-Painful procedures are a necessary part of pediatric care. While health care professionals currently regard pain as a multidimensional phenomenon requiring assessment and treatment, our knowledge regarding the role of parental presence in ameliorating painful experiences for infants and children is limited. The purpose of this study was to assess the attitudes of parents, nurses, and pediatricians regarding parental presence and to determine current practice in our area.

Methods. - Questionnaires were sent to 212 pediatricians in the Intermountain area and to 59 randomly selected nurses who were working on inpatient units at the University of Utah Center for Health Sciences, Salt Lake City, or the Primary Children's Medical Center, Salt Lake City. Outpatient nurses were recruited by including a nurse's questionnaire with those sent to community physicians. Parents were recruited while waiting in the renal, pulmonary, and hematology-oncology clinics at the University of Utah Center for Health Sciences and the Primary Children's Medical Center, Salt Lake City and in four private offices. All 77 parents who were asked to participate completed the questionnaire.

Questionnaires were designed to assess the attitudes and experiences of physicians, nurses, and parents regarding parental presence during medical procedures and to obtain demographic data. Procedures studied included immunizations, blood draws, sutures, intravenous access, lumbar punctures, roentgenography, and trauma evaluations in the conscious and unconscious child. Data were analyzed using the χ^2 and Student's t tests, where appropriate.

Results. - One hundred fifteen of 212 questionnaires to pediatricians and 92 of 173 questionnaires to nurses were returned. Because not all were complete, the data reported reflect only those questions answered.

Of the physicians, 61% are general pediatricians and 31% are subspecialists; 46% are university based and 48% are in private practice; 16% are house officers; 19% have been in practice less than 5 years; and 75% are also parents. Of the nurses responding, 44% are hospital based and 56% are clinic based; the mean number of years in nursing is 9.6, and 73% of the nurses are parents. Of the parents, 97% are married; their median annual income is between \$20 000 and \$30 000 and they average 3.4 children per family.

Regarding parental presence during procedures, 58% of the pediatricians reported that they encourage parents to remain, 18% encourage parents to leave, and 24% leave the decision to the parents. In those cases where the pediatrician encourages the parents to remain, the child's age is not a factor; however, as the perceived degree of invasiveness increases, a greater percentage of physicians excluded parents (eg, the percent of parents excluded for immunizations, the percent excluded for trauma in the unconscious child). No differences were found comparing the responses of generalists and sub-

specialists.

House officers were more likely than practicing physicians to discourage par-

ents from remaining (P = .03). Reasons given include a lack of self-confidence, a belief that parents will be distracting, and a concern that the child will blame the parent for the procedure.

Parental factors, such as parental choice, parental assertiveness, and the physician/patient relationship, were the most important influences on whether physicians included them. Child factors, such as the child's choice and the child's state, were the next most frequently cited.

Nurses also reported that they were more likely to permit parental presence than to prohibit it. During procedures perceived as being more invasive, inpatient nurses would be less likely to allow parents to remain than outpatient nurses (P < .05). Although the pediatricians reported otherwise, nurses perceived that physicians encourage parental presence primarily because of child factors and exclude parents because of their potential interference. No differences were found in comparing the responses of physicians and nurses who were parents and those who were not.

Parents confirmed that they are present during a variety of procedures: more than 90% remained for immunizations, stitches, and blood draws; 75% remained during intravenous access, electrocardiography, and lumbar punctures; and 65% remained during electroencephalography and bone marrow studies. Only during roentenographic procedures were more than 80% of parents excluded. Parents perceived that pediatricians encouraged parental presence primarily for the comfort of the child and only secondarily to please them. The overwhelming response was that parents wanted to remain. Only 2% felt that they would be too upset to benefit their child, although a majority believed pediatricians excluded them for fear of their overreacting or interfering. When asked how pediatricians could help the child cope with a procedure, the majority said an explanation to the child and the parent would be most helpful.

Comment. - There is a dearth of literature addressing parental presence during procedures. Early anesthesia and dental literature suggests that parents are often not given a choice and that children want parents to remain. Two studies indicated that preschool children systematically vary their overt pain behaviors in different social contexts. Children aged 2 to 6 years assigned to "accompanied" or "separated" groups during painless anesthesia induction were less anxious when a parent was present. No instance of objection-

able behavior by a mother was identified.2 Among 18-month-old and 5-yearold children undergoing immunization. half of whom were separated and half were not, there was more crying in both age groups when the mother was present.3 The authors suggested that children may express pain overtly when their mothers are present due to subtle cues expressed by mothers and past reinforcement in painful situations.

Our findings indicate that practicing pediatricians and nurses believe they encourage the presence of parents during procedures, house staff are more likely to discourage parents, and parents think they can comfort their chil-

dren during a procedure.

Despite physicians' reports of allowing parental presence, parents often felt they were excluded against their wishes. Possibly, this discrepancy arises because the "offer" to the parents to remain is biased by the health care provider's ideas about what is best for the patient. At a time when parents are under stress, they may be too vulnerable to effectively insist on what they believe is best. Future research should address this issue, as well as what actually occurs with pediatricians, parents, and children during procedures.

We need to better define whether parental presence can ease the trauma, how crying might be interpreted, and how the child views a parent who does not intervene to stop a procedure. Both theoretical and clinical training programs need to be developed to help residents become more comfortable and facilitate the interaction that parents and children can share during procedures.

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This report was presented at the Ambulatory Pediatrics Association Annual Meeting, May 4, 1989, Washington, DC.

Reprint requests to the Department of Pediatrics, University of Utah Medical Center, 50 N Medical Dr, Salt Lake City, UT 84132 (Dr Merritt).

^{1.} Hanna WJ, Sherlock H. Recall and fears of anaesthesia and surgery in 50 Jamaican paediatric patients. West Indian Med J. 1983;32:75-82

^{2.} Schulman JL, Foley JM, Vernon DT, Allen DA. Study of the effect of the mother's presence during anesthesia induction. Pediatrics. 1967; 39:111-114.

^{3.} Shaw E, Routh D. Effect of mother's presence on children's reaction to aversive procedures. J Pediatr Psychol. 1982;7:33-42.

Gonadal Steroids and Somatic Growth

Sir.—The article by Campos and MacGillivray¹ in the August 1989 issue of AJDC suggested that gonadal steroids did not influence the somatic growth of the 18 children in the study. The graph that accompanies the article and the statement that the final adult height closely approximated or exceeded midparental height supports this suggestion. However, I suggest that more substantial evidence would have included a bone age at the beginning of sex steroidal therapy and a projected height based on the chronologic bone age before the onset of treatment. A demonstration that the final adult height closely approximated or exceeded the projected height would perhaps be a better demonstration of the hypothesis of their article.

> STANLEY G. MORRISON, MD Lincoln Family Medical Group 800 Douglas Rd Stockton, CA 95207

1. Campos SP, MacGillivray MH. Sex steroids do not influence somatic growth in childhood. AJDC. 1989;143:942-943.

In Reply. - The focus of our study was to assess the role of gonadal steroids in the growth of prepubertal children. Growth following replacement sex steroid therapy and adult heights were of secondary importance.

Projected adult heights based on chronologic bone age at the start of sex steroid therapy are less meaningful than actual final heights because of inherent errors in estimating final heights from bone age films.

SUSANA P. CAMPOS, MD MARGARET H. MACGILLIVRAY, MD Division of Endocrinology Children's Hospital of Buffalo 219 Bryant St Buffalo, NY 14222

Informed Consent for Lumbar **Puncture: An Alternative**

Sir. - We read with interest the article by Botkin¹ in the August 1989 issue of AJDC on informed consent for lumbar puncture. In discussing the scenario involving parental refusal of lumbar puncture despite clear medical indications, Botkin recommends that lumbar puncture and treatment proceed without consent unless a court order can be obtained promptly. In practicality, it is difficult to have the parents relinquish their child for a procedure that they strongly oppose, and it is equally difficult and very time-consuming to physically restrain parents in that situation.

Another approach that we have used on occasion when a parent refuses an essential diagnostic study, such as a lumbar puncture, is to begin empiric treatment and admit the child to the hospital. Often the parents may be adamant in refusing the diagnostic test (for a wide variety of reasons) but are willing to allow blood work and intravenous antibiotics. In the case of suspected meningitis, if the degree of suspicion is so high as to warrant the taking of the child from the parents, then immediate treatment is more appropriate than struggling with parents over a lumbar puncture.

Once treatment has been initiated, more discussion with the parents may reveal parental fears about the lumbar puncture, and keep the parents as allies rather than adversaries.

JEFFREY R. AVNER, MD STEVEN M. SELBST, MD Pediatric Emergency Care Associates Children's Hospital of Philadelphia 34th Street and Civic Center Boulevard Philadelphia, PA 19104

1. Botkin JR. Informed consent for lumbar puncture. AJDC. 1989;143:899-904.

In Reply. - The option of initiating treatment for a child with suspected meningitis without performing a lumbar puncture is not a good one from the narrow perspective of the child's health. This approach may lead to unnecessary or inappropriate treatment and it may limit public health measures. Nevertheless, Drs Avner and Selbst's point is well taken. From the broader perspective of the child's welfare and the welfare of the family, this may occasionally be the best of bad options.

There is, of course, a distinction to be made between having the moral authority to override parents' wishes in situations of this type and believing that such an action is right in specific circumstances. Physically wrenching a child from the parents for a diagnostic procedure would be beyond the ability of many physicians who may in good conscience choose the compromise suggested by Drs Avner and Selbst. Should the parents refuse

treatment in such a circumstance, then I would hope Drs Avner and Selbst and others would be willing to protect the child with the judicious use of force, if necessary. The practice of medicine is complex, and physicians must carefully balance the competing considerations of the specific problem at hand. My article was intended to provide guidance on the ethical and legal issues but was not intended to establish inflexible rules of conduct.

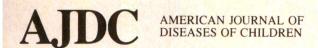
JEFFREY R. BOTKIN, MD, MPH Department of Pediatrics Center for Biomedical Ethics 3395 Scranton Rd Cleveland, OH 44109

Revised Pediatric Code Card

Sir. - A pediatric code card based on a survey of pediatric residency programs in the United States was presented in the January 1988 issue of AJDC1 and readers were invited to make suggestions or recommendations for revisions of that card. Since publication of the code card, the Committee on Drugs of the American Academy of Pediatrics (AAP) has published guidelines on emergency drug doses for infants and children,2 including a clarification on the dose of naloxone.3 These and other developments in pediatric emergency care have prompted us to develop a revised pediatric code card (Figure).

Many excellent suggestions for revisions of the code card have been made by readers of AJDC who corresponded with the author of the original report. Among the many suggestions that have been incorporated are the following: a comma after the 10 in epinephrine 1:10,000; listing all drugs in the generic form rather than by brand name, eg, phenytoin instead of Dilantin; the addition of diazepam (Valium); and a clarification of the "Rule of Drips" section. The authors wish to thank the correspondents for their helpful suggestions.

The drug doses listed on the original code card came from a wide variety of sometimes conflicting sources, including other code cards, textbooks of pediatric emergency medicine, and the common practice of physicians who reviewed the card. The code card has been revised to make drug doses conform to the AAP Committee on Drugs' guidelines; eg, the revised card lists a digitalizing dose of 20 to 40 µg/kg as stated in the AAP guidelines, rather than the 25 to 50 µg/kg listed



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- Geller RJ, Fisher JG: The role of symptomatic therapy for the common cold. J Respir Dis 1987;8(1):20-34.
- 3. Medon PJ, Holshouser MH: Self Medication: Antitussives. *Pharmacy Times* 1985;51(1):80-90.

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CONTRAINDICATIONS: PediaProfen should not be used in patients who have previously exhibited hypersensitivity to ibuprofen, or in individuals with all or part of the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents.

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Studies to date have not identified any subset of patients not at risk of developing peptic ulceration Studies to date have not identified any subset of patients not at risk or developing peptic ulcertation and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in this population. Studies to date are inconcursive concerning the relative task of various NoArds in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be antici-pated to offset the potential increased risk of GI toxicity.

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Fluid retention and edema have been reported in association with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension

Pedia Profen, like other nonsteroidal anti-inflammatory agents, can inhibit platelet aggregation, but the effect is quantitatively less and of shorter duration than that seen with aspirin. Ibuprofen has been shown to prolong bleeding time (but within the normal range) in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying hemostatic defects, PediaProfen should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients on **PediaProfen** should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

In order to avoid exacerbation of disease of adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ibuprofen is added to the treatment program.

The antipyretic and anti-inflammatory activity of **PediaProlen** may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfectious, noninflammatory painful conditions.

Since ibuprofen is eliminated primarily by the kidney, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation. Prospective studies on the safety of ibuprofen in patients with chronic renal failure have not been conducted.

Safety and efficacy of Pedia Profen in children below the age of 6 months has not been established.

Pregnancy: Reproductive studies conducted in rats and rabbits at doses somewhat less than the maximal clinical dose did not demonstrate evidence of developmental abnormalities. However, animal reproduction studies are not always predictive of human response. As there are no adequate and well-controlled studies in pregnant women, this drug should be used during pregnancy only if clearly needed. Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovas-cular system (closure of ductus arteriosus), use during late pregnancy should be avoided. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats. Administration of **PediaProfen** is not recommended during pregnancy.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with ibuprofen is gastrointestinal. In controlled clinical trials, the percentage of adult patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

Adverse reactions occurring in 3% to 9% of patients treated with ibuprofen: nausea, epigastric pain, heartburn, dizziness, rash. Adverse reactions occurring in 1% to 3% of patients: diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract, headache, nervousness, pruritus, tinnitus, decreased appetite, edema, fluid retention (generally responds promptly to drug discontinuation). Still other reactions (less than 1 in 100) have been reported, and are detailed in the full summary of prescribing information.

DOSAGE AND ADMINISTRATION: Shake well prior to administration.

Fever Reduction in Children 6 months to 12 years of age: Dosage should be adjusted on the basis of the initial temperature level (See CLINICAL PHARMACOLOGY for a description of the controlled clinical trial results). The recommended dose is 5 mg/kg if the baseline temperature is less than 102.5 °F or 10 mg/kg if the baseline temperature is greater than 102.5 °F. The duration of fever reduction is generally 6-8 hours and is longer with the higher dose. The recommended maximum daily dose is

Mild to moderate pain: 400 mg every 4 to 6 hours as necessary for the relief of pain in adults

In controlled analgesic clinical trials, doses of ibuprofen greater than 400 mg were no more effective

HOW SUPPLIED: PediaProfen Ibuprofen Suspension 100 mg/5 ml (teaspoon) —

orange, berry-vanilla flavored Bottles of 4 oz (120 ml) NDC 0045-0469-04NDC 0045-0469-16 Bottles of 16 oz (480 ml)

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SHAKE WELL BEFORE USING. Store at room temperature. Caution: Federal law prohibits dispensing without prescription.



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The Pediatric Forum

This department of AJDC is reserved for comment, criticism, observation, and discussion of "issues of current concern and importance for children's health." The Editor encourages our readers to express themselves on a variety of topics and issues. Further, we encourage the submission of unique and brief clinical and scientific observations that do not fulfill the criteria for original articles.

Dialogues With Henry

July 1989

I dreamed that I died last night. It wasn't a pleasant feeling. I was floating in the air above my body. It was lying in a coffin. It was peaceful for a few seconds, lying there. But then I realized what was happening. I woke up and couldn't go back to sleep.

I've dreamed about dying before, but never like this. Like I'd be in a big battle, shooting down the enemy with a machine gun . . . and then being shot. But this dream was different.

I can't believe this is happening to me. It doesn't seem real. I feel like I'm in a haze. If you told me 2 weeks ago that I would be this sick, this soon, I'd have said you're crazy. I mean, here I am, talking about dying.

Every friggin' day is worse. Every day when I don't get better is like another nail being driven into my cof-

I feel so weak. I don't even feel like getting up to take a dump. Can you believe it? Something natural like that? Shit. I don't even want to do that. I feel dizzy when I get up. Really woozy, like I'm very drunk.

I hate waking up in the morning and feeling choked. Sometimes I don't want to wake up.

I had no idea it would be this bad. I thought I'd be sick for a week or two and that would be it. When I came in for cleanouts I thought, geez, this is really bad—I have to miss school—I miss my friends. But I didn't know how bad it could be.

This really sucks.

When we talked 3 years ago, all I was worried about was who I was going to take to the freshman prom. How easy that was.

I'm not even coughing well anymore. It used to be so easy. I would come in for a cleanout and then in a few days I would be back on my feet. No big deal. I guess things get harder when you get older.

I'm glad I lived 20 years. I wouldn't do anything differently. I had a good life, good friends. Maybe tonight I'll write little notes to my parents and friends. You know, personal notes. If I feel up to it.

I don't think I'm going to make it out through the front doors of the damn hospital. It's like a little voice inside me, telling me that. It's not that I've given up hope. It's just this little voice. You know what I mean?

June 1989

Am I going to make it?

I don't know. What you've got to try to do today is to receive as much chest physiotherapy as possible. You're getting antibiotics and other drugs to help you breathe.

There is an old proverb: Parting is a little death. It's so true.

I want you to know that our relationship will spur me to find a treatment for this disease.

I'm glad. I hope you find it. Even if it's too late for me.

You won't be forgotten.
That's what people tell me.

March 1986

What bothers me most about my disease is that I can't keep up with my friends. Like when we're walking I have to slow down after a while and they have to slow down and walk with me.

I used to pretend that I wasn't sick and would give my mother a hard time. But now I've accepted my illness. I make sure to do my physical therapy every day because it's for my own good. I guess I've grown up.

I sometimes think about dying. I wonder how it's going to happen. Am I going to be driving a car and just drop dead? Or am I going to get really sick one day? When a friend of mine died last year it really put me off the track for a week. But it doesn't bother me all the time. When I talk with other sick kids we never talk about it. We all know what it's about.

If I met a 10-year-old kid with my disease, I wouldn't want to tell him anything in particular. I wouldn't want to scare him.

If it weren't for my illness I would want to be an airplane pilot. But right now I want to be a phlebotomist . . . after I finish high school.

I want to get married. I would marry someone who would understand me and my disease. I would never have kids because I wouldn't want them to go through what I've gone through, and I wouldn't want to go through it as a parent. I suppose it would have been better if I hadn't been born. It would have been easier on my parents and me.

But I've never felt like calling it quits. Sometimes, when I see another kid throw their life away—like doing drugs—and they'll probably die in an accident, I wish that they had my disease instead of me.

I don't want to be a burden on my parents. It's hard for them to come to the hospital every day. I don't even like the ride here every 3 months. They never had any children after me. My parents were divorced the same year that my disease was diagnosed. They've both remarried but still don't have other kids.

August 1983

Look at that fountain with all those coins!

Do you know why there are pennies in there?

Sure. People make wishes there. You know what I would wish for if I had one wish?

Something serious? Something serious.

Tell me.

I would wish for a cure for cystic fibrosis.

I hear you.

Can I have a penny?

This article is based on interviews conducted at Massachusetts General Hospital, Boston.

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Stress in Residency

Sir.—In the February 1989 issue of AJDC, Dr Hoekelman¹ discussed sources of stress in pediatric residency and suggested possible ways in which

it can be reduced. Dr Hoekelman listed eight sources of stress that included learning to be a physician, having a family, having relatively low income, and being in a highly competitive environment. Dr Hoekelman suggested that reduction of stress would occur if each resident had an advisor, if 4 weeks' vacation were given each year, and if consecutive hours of work numbered no more than 29. He also suggested that a reduced schedule option be available, that maternity and paternity leaves be granted, and that residents organize and participate in social events with the faculty.

I am a practicing pediatrician in a group of seven pediatricians, and I found this article disturbing. I have always considered residency to be a preparation for the practice of pediatrics. If my experience in practice is representative, pediatric practice is inherently stressful. Each member of our group works 50 hours per week of patient time, and, if overnight call is included, 60 hours per week. Since we attend all cesarean sections, and a disproportionate number of them seem to occur between midnight and 6 AM, I believe that the members of our group would include the overnight hours in calculating our work schedule. We also answer an average of six or seven telephone calls after our office closes at 10 PM and take care of any emergency that comes into our emergency department during the night.

This schedule is more stressful than my colleagues and I would like at times. Coming into the office the next day after being up all or part of a night can be very difficult. However, we follow this system primarily because, in our opinion, it provides continuity and the best quality of care to the children we treat. If we were to evaluate and treat a child with meningitis at midnight and then tell the parents that another physician would take over in the morning because our shift was over, the patient would be ill served, in my opinion.

In other words, pediatric residencies need to be stressful precisely because private practice is stressful. Furthermore, the question needs to be "What is best for the patient?" not "What is easiest for the physician?"

The number of people going into the full-time practice of pediatrics seems to be declining. There could be many reasons for this decline. Perhaps they

are being taught to avoid stress, that they will not be able to handle stress, and that they should choose a career that is "easier." The sources of stress listed in the first paragraph have not changed since the early 1960s when I began medical school and are unlikely to change. It is tough becoming a physician. It should be tough.

Would the result of changes recommended by Dr Hoekelman not change the entire way pediatrics is now practiced? Do we really want to create a bunch of "9-to-5" physicians? Has everyone given enough thought to how the patient is best served? If this article reflects the thinking of others in academic medicine, the issue should be carefully reexamined.

Unless and until we find a way to practice caring and quality pediatrics without stress, our pediatric residency programs need, properly, to be stressful and indeed to train the physicians to cope with stress rather than avoid stress.

JOHN T. BENJAMIN, MD Pediatric Associates 1011 E Jefferson St Charlottesville, VA 22901

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In Reply.—One might think after reading Dr Benjamin's letter that he and I are at opposite ends of the pole on the issue of reducing stress in residency training. Actually, we are

Dr Benjamin and his six partners put in, on average, a 60-hour workweek and go to work on days after they have been up taking care of patients for part or all of the preceding night. They have a stressful schedule, working 20 hours a week more than most people. Dr Benjamin feels that residency training programs should be stressful to prepare physicians to cope with the stress they will face when they enter practice.

The question is, how stressful does a residency need to be to teach young physicians how to cope with stress? Do they need to work more than 80 hours a week (as Dr Benjamin did when he was a resident) to prepare them for a 60-hour workweek in practice? New York State Department of Health regulations in effect since July 1989 limit the number of consecutive hours a resident can work in direct patient-care activities to 24 and the number of hours worked per week to

80, when averaged over a 4-week period. That is far more than Dr Benjamin and his colleagues work. Young physicians fresh out of training who are recruited to Dr Benjamin's practice will consider their new schedule much less stressful than the one they had the previous 3 years, and they will be prepared to cope with it.

Dr Benjamin asks that, in designing residency schedules, we consider what is best for the patient rather than what is easiest for the physician. I don't think the two positions can be separated. Exhausted physicians render poor patient care. While continuity of care is desirable over time, discontinuity of care (transferring responsibility of care from one physician to another) in acute illness situations has never been proved to be bad for patients. Indeed, it makes sense to have a well-rested physician take over, particularly if the patient has a critical illness that requires the application of complicated diagnostic and therapeutic procedures.

As pediatricians, we apply the concepts of health promotion and disease prevention. Training program directors need to apply these same concepts when designing pediatric residents' work schedules.² Directors have a responsibility—a very heavy one—to bring their trainees to a high degree of clinical competence in a way that does not interfere with a reasonably balanced life-style for the residents both during and after training, and in so doing, avoid the poor interpersonal functioning and impairment of professional performance that afflict so many physicians.³

Finally, I would like to reassure Dr Benjamin that the number of people entering the full-time practice of pediatrics is not declining. There has been a steady growth in the number of office-based pediatricians in the United States from 1964 projected through 19904; between 1988 and 1990 that number was expected to grow from 27855 to 31597. Equally important, the percentage of office-based pediatricians vs total pediatricians, which was 63.9% in 1980, will rise to 67.5% in 1990.

ROBERT A. HOEKELMAN, MD Department of Pediatrics University of Rochester 601 Elmwood Ave PO Box 777 Rochester, NY 14642

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Management of Croup

Sir. - We read with interest the article in the September 1989 issue of AJDC by Skolnik. This article purports "to critically review and synthesize the complete body of English-language literature on the medical treatment of croup and formulate a set of recommendations to guide physicians in making treatment decisions for children with croup who require hospitalization." Unfortunately, the article is woefully lacking in terms of management decisions that must be made in some critically ill children with croup. From the outset, Dr Skolnik misrepresents the true nature of the disease entity. He defines croup as a syndrome of larvngeal obstruction when, in fact, it is generally recognized to be a diffuse inflammatory condition of the larynx, trachea, and bronchi. In many circles, the term laryngotracheobronchitis is much preferred to the term croup. In his review, Dr Skolnik tends to neglect the tracheal and bronchial involvement that many times complicate the management of this form of airway obstruction.

In the most severe cases of those children who require hospitalization, medical management will fail, and further intervention for airway support will be required.²⁻⁴ The issue of intubation is only superficially addressed and, unfortunately, one is left searching the bibliography to fill this

While guidelines have not been established for conversion of intubation to tracheotomy in children with severe croup, the issue should at least be addressed in a review article of this nature. In addition, the use of endoscopy in the determination of when a tracheotomy might be necessary is not addressed. Endoscopy may similarly be important in the evaluation of those patients with recurrent croup in whom a subglottic stenosis may be present. Patients with atypical cases of croup may also benefit from an endoscopic procedure to determine whether there

is a coexistent cause of airway obstruction. In failing to address these important issues, Skolnik's review is incomplete and does not offer the clinician the benefit of a management perspective for those patients who are most severely affected with laryngotrache-obronchitis.

In summary, the points that Skolnik addresses in his article are helpful for the clinician and well supported by his review of the literature. Unfortunately, his rather limited look at this disease process prevents the practitioner from exploring all potential management alternatives.

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 Mitchell DP, Thomas RL. Secondary airway support in the management of croup. J Otolaryngol. 1980;9:419-422.

In Reply.—I want to thank Drs Myer and Holmes for illustrating an important point about critically reading the medical literature. The purpose of my article was, as stated in the introduction, to review the medical, not the surgical, treatment of croup. I chose to define the scope of the article in this way to address treatment concerns for 95% to 99% of children admitted to the hospital with croup. 1-3 The medical treatment of croup has not been comprehensively reviewed in the recent literature.

A review of issues surrounding the topics of intubation, tracheotomy, and endoscopic evaluation, while important, has been done recently, 4.5 but doesn't come under the stated purpose of my article.

NEIL S. SKOLNIK, MD 3901 Conshohocken Ave Apt 2206 Philadelphia, PA 19131

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Growth Velocity Values Measured During Short Observation Periods May Obscure Effects of

Treatment of Growth Failure

Sir.—Growth velocity charts are often used to indicate changes in growth rates over short periods. Eager investigators have a special nurse make a number of measurements in children with growth failure, using a stadiometer every 2 to 3 months after treatment with a hormone, a vitamin, or a special diet, perhaps given by a feeding tube, has been initiated. These measurements are then extrapolated and used with growth velocity standards such as those published by Tanner and Davies.¹

The problem rests with the length of the interval between measurements. Let us assume that they are obtained every 3 months. Growth velocity data are published in centimeters per year. The investigator simply multiplies the result by 4. This also multiplies observer bias and measurement error by 4. Here is a hypothetical example. The measurements in the tabulation below were obtained during a year in which a child would grow a total of 6 cm and, therefore, the mean growth velocity for age indeed is 6 cm/y:

	Observed Growth,	Extrapolated Rate,
Quarter	cm	cm/y
1st	1.5	6.0
2nd	1.0	4.0
3rd	1.6	6.4
4th	1.9	6.6

This looks pretty good on a scattergram. Three values are normal or above, and the one small value, just 4 cm/y, does not seem to be very important. However, the originator of growth velocity standards, J. M. Tanner, MD, DSc, recommended that.

these charts refer to whole-year velocities converted from increments that should be taken over not less than 0.85 years and not more than 1.15 years. Velocities calculated over shorter periods reflect seasonal effects (most children grow faster in the spring and slower in the fall) and are

relatively more affected by the unavoidable errors in measurement (which should not exceed 3 mm).¹

My recommendation is simple. Let us use growth velocity curves for yearly measurements only, and also ask for z scores when we want to document the effect of certain treatments on the growth of individual children. The z score is the patient's height minus mean height for age divided by the SD of mean height for age.

In my view, real catch-up growth is proved only when z scores decrease. No one will argue that a treatment was effective if a child who was 3 SDs below the mean before treatment is found to be just 1 SD below the mean at the end of the observation period. While any method may have shortcomings, in all my studies of children with growth failure, I found it best to use z scores in the analysis of large amounts of growth data.

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Reprint requests to Department of Pediatrics, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (Dr Stickler).

 Tanner JM, Davies PSW. Clinical longitudinal standards for height and height velocity for North American children. J Pediatr. 1985;107: 317-329.

In Reply.—The letter from Dr Stickler addresses two issues: (1) extrapolation of growth patterns from too short observation periods; and (2) use of z scores to document the growth observed in a child, as sequential measurements are examined. There is universal agreement among authorities in biometry that the data analyst should not draw inferences or make predictions outside the boundaries of the observed values. Growth observed for only a few months should not be used to estimate expected growth over a full year.

The use of z scores for evaluating growth status is less universally accepted. A z score is a concise way to express the distance of a particular value from the mean of a normally distributed set of values. A z score of "+1" is 1 SD above the mean; a z score of -1.5 is 1.5 SDs below the mean. This tidy notation has appeal because of its brevity, convenience, and wide applicability. But for many fastidious observers, z scores are fatally flawed.

The z score is an accurate index of

dispersion only if the values are distributed in normal (gaussian) form, which many growth measurements are not. Because growth values (such as weight) are often highly skewed, monographs and other reference documents may use percentiles rather than mean and SD to describe sets of body measurements.

This is more than mere pedantry. An example using data from the National Center for Health Statistics (NCHS)² may help. A girl aged 7 years with weight at the fifth percentile for her age has a z score of -1.5. At 10 vears of age, with weight still at the fifth percentile, her z score is -1.1. She was at the fifth percentile each time she was weighed. Relative to other girls of her age, she grew in a consistent weight channel. The change in her z score suggests that she had changed her growth track. The theory supporting z scores (normality) does not consistently accord with actual observation (skewness). The differences between theory (z scores) and empiric observation may be dismissed by some analysts as being "close enough." Nevertheless, the issue of normality should be discussed whenever z scores are used.

The growth data from NCHS² are presented in large tables and charts that employ seven percentile points. If means and SDs (*z* scores) were appropriate for describing growth data, their use in the NCHS publication would have greatly reduced its size and complexity. The observed growth data were not normally distributed, so NCHS was obliged to use percentiles.

In short, Dr Stickler's point about extrapolation of growth velocity from short observation periods is important; his assertions about z scores are less persuasive, in my opinion.

George W. Brown, MD Los Lunas, NM

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High-Dose Intravenous Gamma Globulin Infusions in Hemolytic-Uremic Syndrome: A Preliminary Report

Sir.—The classic form of hemolyticuremic syndrome (HUS) follows a prodrome of bloody diarrhea due to verotoxin-producing Escherichia coli

infection.1 Verotoxin damages endothelial cells² and releases factor VIII, von Willebrand factor (vWF) antigen, and large multimers of vWF.3 These large vWF multimers, in the presence of a platelet agglutinating factor, may facilitate platelet aggregation, resulting in microthrombi and thrombocytopenia. A platelet agglutinating factor has been reported in HUS4 and can be inhibited by IgG obtained from adults only.4,5 Anecdotal reports suggest a beneficial effect of intravenous infusions of human gamma globulins (IVGG) in thrombotic thromboeytopenic purpura.6 Because the inciting factors and clinical manifestations of thrombotic thrombocytopenic purpura and HUS are similar, it is likely that both represent a spectrum of disease with a common mechanism7 and both might improve with IVGG therapy.

In our preliminary study, eight consecutively treated children (three boys, five girls; mean age, 3.75 years) with classic HUS and initial platelet counts of less than $100 \times 10^{\circ}$ /L received infusions of IVGG (Sandoglobulin), 400 mg/kg per day for 5 days. The severity of HUS, as classified by Gianantonio et al, was mild in three children, moderate in three children, and severe in two children.

The course of HUS in the children treated with IVGG infusions was compared with that in two historical groups of children with classic HUS previously seen by us. A group treated with fresh-frozen plasma (FFP) infusions was composed of 12 children-5 boys and 7 girls with a mean age of 4.75 years-with mild (6 children), moderate (4 children), or severe (2 children) HUS. A control group consisted of 23 children-8 boys and 15 girls with a mean age of 3 years-with mild (12 children), moderate (7 children), or severe (4 children) HUS who had received neither FFP nor IVGG (Table). These 35 children were from a group of 47 children with HUS treated from 1972 through 1985. Of the 12 children excluded, there were 9 whose initial platelet counts were 100 × 10°/L or more, a criterion set to exclude IVGG therapy; 2 children were unavailable for follow-up; and 1 child had HUS associated with the onset of metastatic Wilms' tumor. The criteria for dialysis, such as anuria, volume overload, serum electrolyte abnormalities, and the severity of renal failure, were the same for all three groups. Packed red blood cells were transfused as required for a he-

matocrit value less than 0.20/L. The response to treatment was evaluated by (1) hematologic improvement by resolution of thrombocytopenia (rise in daily platelet count) and anemia (need for packed red blood cell transfusion to maintain a hematocrit value more than 0.20/L) and (2) renal function improvement by achievement of urine volume greater than 1 mL/kg per hour, reduction of serum creatinine less than 88 µmol/L, and the number of days that dialysis was required. The effect on long-term sequelae of HUS, such as hypertension, development of end-stage renal disease, and residual neurological abnormalities (ie, persistence of seizures requiring medications, abnormal electroencephalogram readings, persistent abnormalities on computed tomographic studies or radionuclide brain scans, and physical handicap) at the end of 2 years was compared. Deaths in each group were recorded. Severity of the HUS and male-to-female distribution in separate groups were evaluated by x2 analyses. Daily platelet counts were evaluated by Student's unpaired t test. Changes in platelet count during a period of 8 days in each of the three groups were analyzed9 to assess the trend in the increase of platelet counts. P<.05 was considered significant.

Treatment with IVGG was associated with statistically significant improvement in platelet counts in comparison with FFP treatment (P < .05)and controls (P < .01) (Figure) and the trend of increase in platelet counts in comparison with FFP treatment (P<.05) or no therapy (P<.001). Urine output increased significantly faster in the IVGG group compared with the control group (P < .05). Although the decrease in serum creatinine was faster with IVGG than FFP infusions when compared with the controls, it did not reach a statistically significant level. Transfusion and the length of dialysis requirements were not different. Long-term residua were absent with IVGG infusions (Table).

There were no adverse effects of IVGG or FFP infusions. Our preliminary data suggest that a total dose of 2 g/kg of IVGG infused over 5 days improved thrombocytopenia and shortened periods of oligoanuria and elevated serum creatinine in HUS. Both long-term morbidity and mortality also improved, suggesting possible therapeutic benefits. Additionally, the treatment was relatively safe.

The exact mode of action of IVGG

Effects of Intravenous Gamma Globulin (IVGG) Infusions on Resolution of Hemolytic-Uremic Syndrome (HUS)*

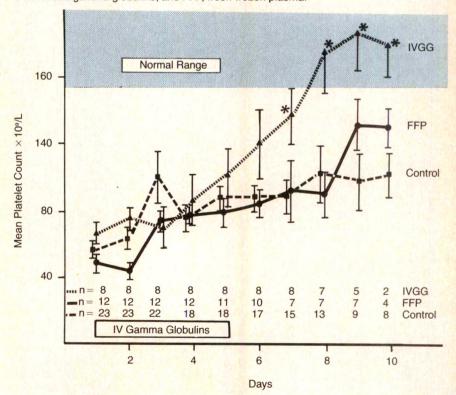
	IVGG (n = 8)	FFP (n = 12)	Control (n = 23)
Age, y Mean (Range)	3.75 (2-9)	4.25 (0.5-9)	3 (0.5-9)
Sex, M/F	3/5	5/7	8/15
Severity of HUS,† mild/moderate/severe	3/3/2	6/4/2	12/7/4
Acute phase‡ Units of packed red blood cells transfused	5.6±1.0 (8)	5.0±1.1 (11)	4.0 ± 0.7 (21)
No. of days for Urine volume, >1 mL/kg per h	5±1.0 (5)§	6.9±1.6 (7)	9.6±1.9 (14)
Serum creatinine, <88 µmol/L	16±4.3 (7)	34±10.2 (10)	47.9±20.9 (15)
Dialysis	7.6 ± 0.9 (5)	6±1.2 (8)	7±1.1 (13)
Long-term sequelae Hypertension for >2 y	None	1/11	2/21
End-stage renal disease	None	1/11	2/21
Neurologic residua	None	5/11	5/21
Deaths	None	1/12	2/23

^{*}There were no significant differences between the groups as evaluated by Student's t test and χ^2 analysis. FFP indicates fresh-frozen plasma.

†Severity of HUS as described in text.8

One-tailed P>.05

Daily platelet count (mean \pm SEM) in patients with hemolytic-uremic syndrome. Numbers of patients decreased as those who reached a platelet count of greater than $150 \times 10^{\circ}$ /L were excluded. Boxed area labeled "IV Gamma Globulins" represents 5-day treatment in IVGG group only. Shaded area represents the normal range for platelet counts. Asterisk indicates statistically significant difference (P<.05) as evaluated by Student's t test; IVGG, intravenous gamma globulins; and FFP, fresh-frozen plasma.



[‡]Numbers in parentheses indicate assessable patients. Results expressed as mean ± SEM. §P<.05.

in HUS remains unclear. Intravenous gamma globulin preparations, mostly obtained from pools of adult donors, have shown neutralizing activity against verotoxin in in vitro studies. 10 In 29 of 30 children without HUS. such neutralizing antibodies were absent and may predispose them to infection. 10 Hence, passive transfusion of this specific antibody in patients with HUS may possibly neutralize the verotoxin and shorten the course, and may explain the beneficial effects noted in our study. Alternatively, as suggested in idiopathic thrombocytopenic purpura, IVGG may block Fc receptors on platelets or reticuloendothelial cells and prevent platelet removal.11 A third possibility is that IVGG may inhibit the platelet agglutinating factor, as has been demonstrated in both in vitro3,4 and in vivo3 studies of patients with HUS and thrombocytopenic purpura. Because of the relative safety and possible therapeutic benefits of IVGG, we feel that a randomized controlled trial of IVGG in the early phase of HUS is warranted.

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Late Sudden Unexpected Deaths in Hospitalized Infants With Bronchopulmonary Dysplasia

Sir. —I am a home care physician and read with much concern the report of late sudden unexpected deaths in infants with bronchopulmonary dysplasia who required prolonged mechanical ventilation.1 During the past decade, I have been discharging patients and helping families manage their ventilator-assisted children at home.2 These children were medically stable, as defined by clinical course (no major diagnostic intervention or therapeutic changes within 1 month) and by clinical and physiologic criteria appropriate to age and underlying pathogenesis.3

Cases of patients with bronchopulmonary dysplasia who require home mechanical ventilation are represented in my experiences both in Illinois and in Pennsylvania.^{3,4} Such patients have required months of optimal ventilation as defined by patient eligibility criteria,⁴ and these cases have resulted in excellent outcomes for children who grow and develop and eventually become free of their need for oxygen and the ventilator.

Home mechanical ventilation is an outgrowth of home care for survivors of respiratory paralytic polio and other neuromuscular diseases. After an initial success, it has been applied to other, more difficult conditions, such as high spinal cord injury. Patients with cardiopulmonary conditions represent a greater set of challenges, with different prognoses, risks, and home care organizational and technological requirements.

Although there is a growing interest in home mechanical ventilation for patients with severe bronchopulmonary dysplasia, this option must only be chosen after we understand these differences. There is good reason to believe that abnormal function (ie, airway obstruction, low compliance, low functional residual capacity) exists well into the first year of life, and that it is best not to consider withdrawal of optimal ventilation until well into the second year of life. When these patients receive optimal ventilation (Pco₂ <50 mm Hg, Pao₂ >65 mm Hg, O₂ saturation >93%) they have greater functional reserve and do not exhibit intermittent cyanosis, fever, or other signs of medical instability.

Thus, candidates for home care must be medically managed by strict criteria, with great concern for medical stability. They should not be prematurely considered for home care for cost-containment purposes. Other options, such as specially designated transitional units, may be a cost-effective alternative. The observations by Abman et al¹ make this recommendation all the more important.

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Attitudes Regarding Parental Presence During Medical Procedures

Sir.—Painful procedures are a necessary part of pediatric care. While health care professionals currently regard pain as a multidimensional phenomenon requiring assessment and treatment, our knowledge regarding the role of parental presence in ameliorating painful experiences for infants and children is limited. The purpose of this study was to assess the attitudes of parents, nurses, and pediatricians regarding parental presence and to determine current

practice in our area.

Methods. - Questionnaires were sent to 212 pediatricians in the Intermountain area and to 59 randomly selected nurses who were working on inpatient units at the University of Utah Center for Health Sciences, Salt Lake City, or the Primary Children's Medical Center, Salt Lake City. Outpatient nurses were recruited by including a nurse's questionnaire with those sent to community physicians. Parents were recruited while waiting in the renal, pulmonary, and hematology-oncology clinics at the University of Utah Center for Health Sciences and the Primary Children's Medical Center, Salt Lake City and in four private offices. All 77 parents who were asked to participate completed the questionnaire.

Questionnaires were designed to assess the attitudes and experiences of physicians, nurses, and parents regarding parental presence during medical procedures and to obtain demographic data. Procedures studied included immunizations, blood draws, sutures, intravenous access, lumbar punctures, reentgenography, and trauma evaluations in the conscious and unconscious child. Data were analyzed using the χ^2 and Student's t tests, where appropriate.

tests, where appropriate.

Results.—One hundred fifteen of 212 questionnaires to pediatricians and 92 of 173 questionnaires to nurses were returned. Because not all were complete, the data reported reflect only those questions answered.

Of the physicians, 61% are general pediatricians and 31% are subspecialists; 46% are university based and 48% are in private practice; 16% are house officers; 19% have been in practice less than 5 years; and 75% are also parents. Of the nurses responding, 44% are hospital based and 56% are clinic based; the mean number of years in nursing is 9.6, and 73% of the nurses are parents. Of the parents, 97% are married; their median annual income is between \$20 000 and \$30 000 and they average 3.4 children per family.

Regarding parental presence during procedures, 58% of the pediatricians reported that they encourage parents to remain, 18% encourage parents to leave, and 24% leave the decision to the parents. In those cases where the pediatrician encourages the parents to remain, the child's age is not a factor; however, as the perceived degree of invasiveness increases, a greater percentage of physicians excluded parents (eg, the percent of parents excluded for immunizations, the percent excluded for trauma in the unconscious child). No differences were found comparing the responses of generalists and subspecialists.

House officers were more likely than practicing physicians to discourage par-

ents from remaining (P = .03). Reasons given include a lack of self-confidence, a belief that parents will be distracting, and a concern that the child will blame the parent for the procedure.

Parental factors, such as parental choice, parental assertiveness, and the physician/patient relationship, were the most important influences on whether physicians included them. Child factors, such as the child's choice and the child's state, were the next most frequently cited.

Nurses also reported that they were more likely to permit parental presence than to prohibit it. During procedures perceived as being more invasive, inpatient nurses would be less likely to allow parents to remain than outpatient nurses (*P*<.05). Although the pediatricians reported otherwise, nurses perceived that physicians encourage parental presence primarily because of child factors and exclude parents because of their potential interference. No differences were found in comparing the responses of physicians and nurses who were parents and those who were not.

Parents confirmed that they are present during a variety of procedures; more than 90% remained for immunizations, stitches, and blood draws; 75% remained during intravenous access. electrocardiography, and lumbar punctures; and 65% remained during electroencephalography and bone marrow studies. Only during roentenographic procedures were more than 80% of parents excluded. Parents perceived that pediatricians encouraged parental presence primarily for the comfort of the child and only secondarily to please them. The overwhelming response was that parents wanted to remain. Only 2% felt that they would be too upset to benefit their child, although a majority believed pediatricians excluded them for fear of their overreacting or interfering. When asked how pediatricians could help the child cope with a procedure, the majority said an explanation to the child and the parent would be most helpful.

Comment.—There is a dearth of literature addressing parental presence during procedures. Early anesthesia and dental literature suggests that parents are often not given a choice and that children want parents to remain. Two studies indicated that preschool children systematically vary their overt pain behaviors in different social contexts. Children aged 2 to 6 years assigned to "accompanied" or "separated" groups during painless anesthesia induction were less anxious when a parent was present. No instance of objection-

able behavior by a mother was identified.² Among 18-month-old and 5-year-old children undergoing immunization, half of whom were separated and half were not, there was more crying in both age groups when the mother was present.³ The authors suggested that children may express pain overtly when their mothers are present due to subtle cues expressed by mothers and past reinforcement in painful situations.

Our findings indicate that practicing pediatricians and nurses believe they encourage the presence of parents during procedures, house staff are more likely to discourage parents, and parents think they can comfort their chil-

dren during a procedure.

Despite physicians' reports of allowing parental presence, parents often felt they were excluded against their wishes. Possibly, this discrepancy arises because the "offer" to the parents to remain is biased by the health care provider's ideas about what is best for the patient. At a time when parents are under stress, they may be too vulnerable to effectively insist on what they believe is best. Future research should address this issue, as well as what actually occurs with pediatricians, parents, and children during procedures.

We need to better define whether parental presence can ease the trauma, how crying might be interpreted, and how the child views a parent who does not intervene to stop a procedure. Both theoretical and clinical training programs need to be developed to help residents become more comfortable and facilitate the interaction that parents and children can share during procedures.

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Gonadal Steroids and Somatic Growth

Sir.-The article by Campos and MacGillivray in the August 1989 issue of AJDC suggested that gonadal steroids did not influence the somatic growth of the 18 children in the study. The graph that accompanies the article and the statement that the final adult height closely approximated or exceeded midparental height supports this suggestion. However, I suggest that more substantial evidence would have included a bone age at the beginning of sex steroidal therapy and a projected height based on the chronologic bone age before the onset of treatment. A demonstration that the final adult height closely approximated or exceeded the projected height would perhaps be a better demonstration of the hypothesis of their article.

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1. Campos SP, MacGillivray MH. Sex steroids do not influence somatic growth in childhood. *AJDC*. 1989;143:942-943.

In Reply.—The focus of our study was to assess the role of gonadal steroids in the growth of prepubertal children. Growth following replacement sex steroid therapy and adult heights were of secondary importance.

Projected adult heights based on chronologic bone age at the start of sex steroid therapy are less meaningful than actual final heights because of inherent errors in estimating final heights from bone age films.

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Informed Consent for Lumbar Puncture: An Alternative

Sir.—We read with interest the article by Botkin¹ in the August 1989 issue of AJDC on informed consent for lumbar puncture. In discussing the scenario involving parental refusal of lumbar puncture despite clear medical indications, Botkin recommends that lumbar puncture and treatment proceed without consent unless a court order

can be obtained promptly. In practicality, it is difficult to have the parents relinquish their child for a procedure that they strongly oppose, and it is equally difficult and very time-consuming to physically restrain parents in that situation.

Another approach that we have used on occasion when a parent refuses an essential diagnostic study, such as a lumbar puncture, is to begin empiric treatment and admit the child to the hospital. Often the parents may be adamant in refusing the diagnostic test (for a wide variety of reasons) but are willing to allow blood work and intravenous antibiotics. In the case of suspected meningitis, if the degree of suspicion is so high as to warrant the taking of the child from the parents, then immediate treatment is more appropriate than struggling with parents over a lumbar puncture.

Once treatment has been initiated, more discussion with the parents may reveal parental fears about the lumbar puncture, and keep the parents as allies rather than adversaries.

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1. Botkin JR. Informed consent for lumbar puncture. AJDC. 1989;143:899-904.

In Reply.—The option of initiating treatment for a child with suspected meningitis without performing a lumbar puncture is not a good one from the narrow perspective of the child's health. This approach may lead to unnecessary or inappropriate treatment and it may limit public health measures. Nevertheless, Drs Avner and Selbst's point is well taken. From the broader perspective of the child's welfare and the welfare of the family, this may occasionally be the best of bad options.

There is, of course, a distinction to be made between having the moral authority to override parents' wishes in situations of this type and believing that such an action is right in specific circumstances. Physically wrenching a child from the parents for a diagnostic procedure would be beyond the ability of many physicians who may in good conscience choose the compromise suggested by Drs Avner and Selbst. Should the parents refuse

treatment in such a circumstance, then I would hope Drs Avner and Selbst and others would be willing to protect the child with the judicious use of force, if necessary. The practice of medicine is complex, and physicians must carefully balance the competing considerations of the specific problem at hand. My article was intended to provide guidance on the ethical and legal issues but was not intended to establish inflexible rules of conduct.

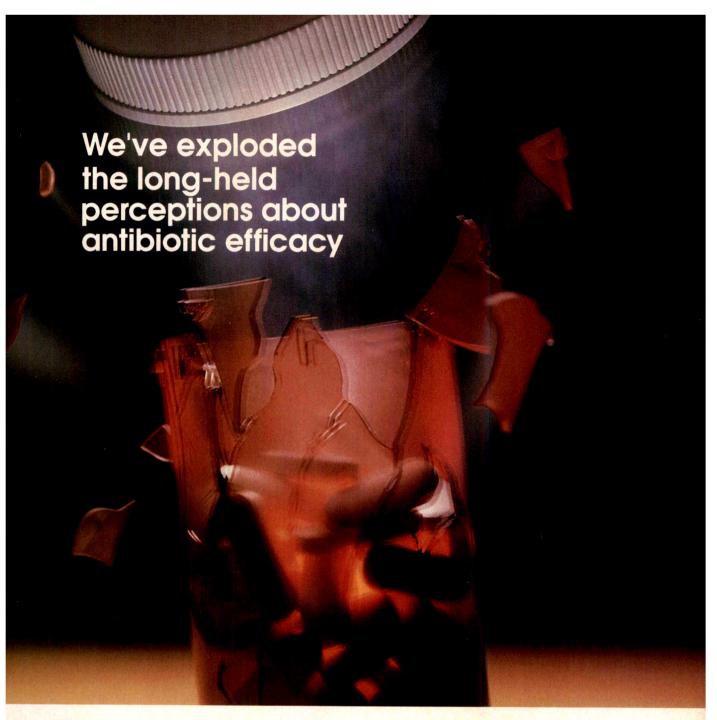
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Revised Pediatric Code Card

Sir. - A pediatric code card based on a survey of pediatric residency programs in the United States was presented in the January 1988 issue of AJDC1 and readers were invited to make suggestions or recommendations for revisions of that card. Since publication of the code card, the Committee on Drugs of the American Academy of Pediatrics (AAP) has published guidelines on emergency drug doses for infants and children,2 including a clarification on the dose of naloxone.3 These and other developments in pediatric emergency care have prompted us to develop a revised pediatric code card (Figure).

Many excellent suggestions for revisions of the code card have been made by readers of *AJDC* who corresponded with the author of the original report. Among the many suggestions that have been incorporated are the following: a comma after the 10 in epinephrine 1:10,000; listing all drugs in the generic form rather than by brand name, eg, phenytoin instead of Dilantin; the addition of diazepam (Valium); and a clarification of the "Rule of Drips" section. The authors wish to thank the correspondents for their helpful suggestions.

The drug doses listed on the original code card came from a wide variety of sometimes conflicting sources, including other code cards, textbooks of pediatric emergency medicine, and the common practice of physicians who reviewed the card. The code card has been revised to make drug doses conform to the AAP Committee on Drugs' guidelines; eg, the revised card lists a digitalizing dose of 20 to 40 µg/kg as stated in the AAP guidelines, rather than the 25 to 50 µg/kg listed



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CLINICAL PHARMACOLOGY

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72 hours after application.

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The Editorial Board Speaks . . .

William W. Waring, MD





"Will" Waring joined AJDC on our transfer to New Orleans. He is a consummate academician who everyone at Tulane University recommended to me for the position of Associate Editor. Will received his education at Yale University and Harvard University, and did his residency at Children's Hospital in Boston and The Johns Hopkins Hospital in Baltimore. He then joined the Tulane faculty in 1957 and became the Jane B. Aron Professor of Pediatrics in 1986. His major interests are in pediatric pulmonology, with special emphasis on cystic fibrosis. He has written and spoken extensively in these areas, and is an internationally regarded specialist. Will has been a member of major national and international scientific groups, and has been a leader and moving force for many of these. He is married to Nell Pape Waring, MD, an allergist, also on the Tulane School of Medicine faculty, and they have five children, William, Jr, Benjamin, Antonio, Peter, and Patrick.

GAUDETE!

During my senior year in medical school, I had to write and deliver a paper to an undergraduate medical society. After much thought, I chose cystic fibrosis as my topic. It was a "hot disease." Although undoubtedly sickening and killing people for millennia, cystic fibrosis had been recognized a mere decade previously. Investigators in New York and Boston had sharply differing views on the pathogenesis of its pulmonary manifestations. Andersen and Hodges2 at Columbia University felt strongly that vitamin A played a key role, whereas Farber³ at Harvard University had coined the term mucoviscidosis to describe what he believed was an inborn disease of all mucus-secreting glands.

In preparing my paper I was able to read the entire world's literature on the subject, and for a brief heady moment knew everything that had been published about the disease. (I have been falling farther and farther behind since then.) As boring as that paper was, in retrospect it was crucial in my pediatric career. It helped me identify a vocational goal.

A few years later, as a fledgling pulmonary subspecialist, I found myself taking care of children with cystic fibrosis—just a few at the beginning, but more and more as the years passed. Most of them grew and flourished for awhile but then withered as they began to run out of functioning alveoli. During all those years, former patients and new ones inevitably and imperceptibly became part of me-hospitalizations, picnics, chest tubes, clinic visits, lobectomies, graduations, marriages, intestinal obstructions, funerals. I can never forget the Madelines, Rhondas, Vivians, Joes, Missys-or their courageous, wonderful parents.

Treatments came and went, including the nightly mist tent. From time to time there would be sporadic claims of "breakthroughs" that were never such. Hopes of patients and their families would flare, only to be doused. "No, Joe, selenium deficiency is not the cause of cystic fibrosis." However, clinical advances did take place. Enteric-coated pancreatic enzymes permitted liberalization of diets. Powerful antimicrobial agents for flare-ups of chronic Pseudomonas aeruginosa pulmonary infections were clearly beneficial. But progress always seemed slow, especially at the time of clinic visits when I would try to tell parents what seemed to be new and promising.

But now, after all those years of waiting, this past September something really happened that does constitute a magni-

tude 9 breakthrough on a scale from 1 to 10—the discovery of the gene for cystic fibrosis,4 not by serendipity, but by methodical, awe-inspiring tracking down of an extraordinarily elusive quarry. The way is now open for much more directed research into, for example, (1) who carries the gene, (2) how the gene works, (3) what other alleles exist, and (4) what the relationships are between the various phenotypes and genotypes of cystic fibrosis.

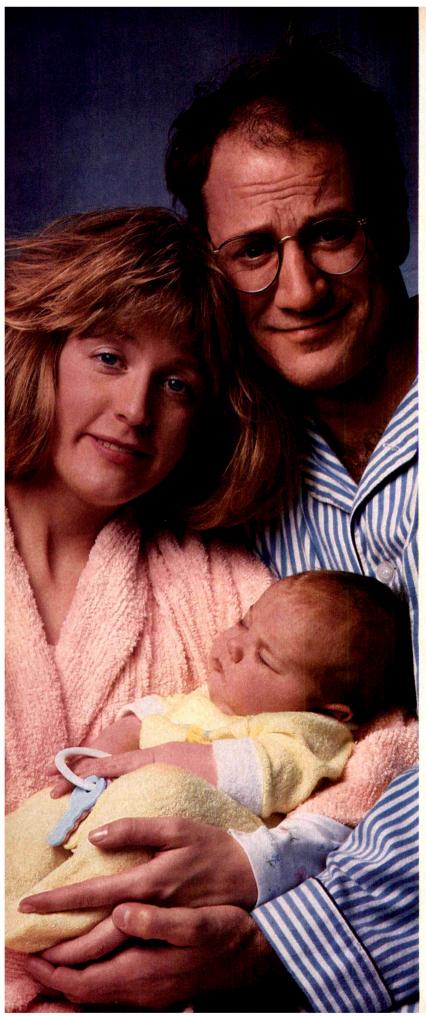
How should one react to this news? It would be a mistake for both patients and physicians, in expectation of a "cure," to slacken the intensity of conventional therapy, which has been responsible for a steadily expanded longevity. Indeed, existing treatment should be intensified with the hope of preserving lung function for as long as it takes. Various multicenter studies of existing but unproved treatment modalities presently under way throughout the country may well offer additional help while waiting for the cure.

Nevertheless, it is now conceivable that some agent will be developed that, when swallowed, ingested, injected, or inhaled, will reverse the presumed chloride channel defect⁵ and thus control the disease. As I talk to patients and their parents, I sense in their manner a new lightness and a new hope. I have those emotions, too! Indeed, it is the first time I have ever permitted myself to feel, much less express, such optimism. Although I have no idea in which way this discovery will be of benefit, I know that it will. Accordingly, I rejoice with everyone who suffers from cystic fibrosis, with all their families and friends, and with all those physicians, nurses, nutritionists, social workers, respiratory therapists, and others who have ever cared for anyone with that disease. And, to the extent that we are all planetary shipmates, I urge you, too, to rejoice.

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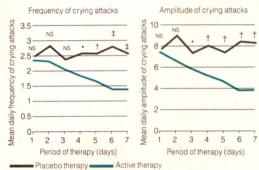
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Articles

Rhesus Rotavirus Candidate Vaccine

Clinical Trial in Children Vaccinated Between 2 and 5 Months of Age

Timo Vesikari, MD; Tarja Rautanen, MD; Tiina Varis, MD; Graham M. Beards; Albert Z. Kapikian, MD

 Live attenuated oral rhesus Rotavirus candidate vaccine (strain MMU 18006 [lot RRV-1]) was evaluated for immunogenicity, safety, and clinical protection in a double-blind, placebo-controlled trial involving 200 infants aged 2 to 5 months when vaccinated. Vaccine-induced fourfold or greater rise of Rotavirus antibodies was seen in 62% of the infants. Febrile reactions of short duration on days 3 and/or 4 after vaccination occurred in 26% of the vaccine recipients. The clinical follow-up covered two Rotavirus seasons, in which serotypes 1 and 4 were prevalent. There were 16 cases of confirmed Rotavirus diarrhea in the placebo-treated group and 10 in the vaccine-treated group; from this a vaccine protection rate of 38% was derived. Clinical severity of Rotavirus diarrhea was assessed by a score; 13 cases in the placebo-treated group and 5 in the vaccine-treated group were regarded as severe or moderately severe, giving a vaccine protection rate of 67%. The rhesus Rotavirus vaccine induces partial protection against heterotypic Rotavirus disease, but the level of protection achieved with the present vaccine dose in this age group appears to be insufficient for a general Rotavirus vaccination.

(AJDC, 1990;144:285-289)

Live attenuated heterologous rotaviruses are candidates for a human Rotavirus vaccine. 14 Cross-protection against human Rotavirus diarrhea was first shown with a live attenuated oral bovine Rotavirus vaccine, which induced more than 80% protection against severe Rotavirus diarrhea in Finnish

infants aged 6 to 12 months. ^{5,6} However, the RIT 4237 bovine *Rotavirus* vaccine proved less efficacious in 2- to 5-monthold Gambian⁷ infants, who, like infants in Rwanda, ⁸ showed a low serological response rate to the oral vaccine.

Rhesus Rotavirus strain MMU 18006 (lot RRV-1) is an attractive alternative for an oral human Rotavirus vaccine, since it is more infectious than the bovine vaccine for humans; ie, a lower dose induces a high rate of serological response. 9-13 This might result in better efficacy, particularly in young infants possessing passively acquired maternal antibodies that may compromise the "take" of a vaccine. Furthermore, the rhesus Rotavirus vaccine strain is closely related to human Rotavirus type 3 by neutralization assay (VP7), whereas bovine Rotavirus (type 6) is distinct from all identified human Rotavirus serotypes. The closer relatedness of rhesus Rotavirus and some human rotaviruses conceivably might result in better cross-protection.9

The rhesus *Rotavirus* candidate vaccine RRV-1 is being tested in several clinical trials in developed and developing countries. Promising results were obtained in a trial in Venezuela, where the vaccine induced a high degree of protection against serotype 3 *Rotavirus* diarrhea in 1- to 4-month-old infants. This report describes the results of a 2-year trial in Finland, carried out in the same setting as previous trials of bovine *Rotavirus* vaccine.

PATIENTS AND METHODS Vaccinees

The infants enrolled in the study were born at the Tampere (Finland) University Central Hospital between July and October 1985 and were living in the city of Tampere or in its neighboring communities. All the families had adequate housing and sanitary facilities and could be regarded as "middle class." The medical records for the neonatal period of

such newborns were reviewed, and full-term infants found healthy at discharge from the hospital were selected. The parents of the infants were approached by a letter asking them to volunteer in the vaccine trial; approximately one third of those approached did so.

All the vaccinees were between 60 and 150 days of age when vaccinated. Before vaccination, the infants underwent physical examination by a participating pediatrician, and those found healthy were approved for the trial. A few infants had runny noses, but without fever, and appeared otherwise healthy; these were also enrolled in the study.

General Design

The study was randomized, double blind, and placebo controlled. The vaccine and placebo preparations (see below) were packed in random order in numbered vials; the code was kept with the Diarrhoeal Diseases Control Programme of the World Health Organization (WHO) in Geneva, Switzerland, and was unavailable to the investigators until the end of the study.

The study protocol was reviewed and approved by the Ethical Committee of the Tampere University Central Hospital and by the National Institute of Allergy and Infectious Diseases Clinical Research Subpanel on Human Studies of the National Institutes of Health, Bethesda, Md. The protocol was also approved by the Scientific Working Group on Immunology, Microbiology and Vaccine Development of the WHO Diarrhoeal Diseases Control Programme, and the study was financially supported by WHO as the sole sponsor.

The vaccinations were carried out between December 1985 and January 30, 1986. The Christmas season interrupted the vaccinations so that 140 infants were vaccinated before Christmas and 60 were vaccinated in January 1986. The study was completed and the code opened at the end of June 1987.

The parents of the participating infants received written and oral information about *Rotavirus* diarrhea, the experimental vaccine, and the nature of the trial. They signed a written consent form approved by the above bodies.

Accepted for publication September 7, 1989. From the Department of Clinical Sciences, University of Tampere, Finland (Drs Vesikari, Rautanen, and Varis); World Health Organization Collaborating Centre for Research and Reference on Rotavirus, Birmingham, England (Mr Beards); and Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Disease, National Institutes of Health, Bethesda, Md (Dr Kapikian).

Reprint requests to Department of Clinical Sciences, University of Tampere, Teiskontie 35, 33520 Tampere, Finland (Dr Vesikari).

Table 1.—Serological Responses (Fourfold or Greater Rise) in Childre	en
Receiving RRV-1 Vaccine or Placebo*	

	No. With Respo	
Serological Test	Vaccine	Placebo
Tube neutralization against RRV	15/25 (60)	0/16 (0)
Plaque reduction neutralization against RRV	46/81 (57)	3/90 (3)
Either test†	61/99 (62)	3/99 (3)

^{*}RRV-1 indicates rhesus Rotavirus vaccine serotype 1.

Vaccine and Placebo

The history of rhesus Rotavirus strain MMU-18006 (RRV-1) has been described previously.9 Briefly, the final vaccine product was passaged 16 times in tissue culture: the first 9 in primary or secondary monkey kidney cells and the last 7 in fetal rhesus lung diploid cells. The vaccine for the trial was supplied by Flow Laboratories, McLean, Va, which prepared it under contract to the National Institute of Allergy and Infectious Diseases, and it was shipped on dry ice. In the study, a 1:100 dilution of the bulk, corresponding to about 10⁴ plaque-forming units (PFU) per milliliter, was used. This vaccine dilution was prepared locally by a technician not otherwise involved in the study. The diluent was Minimum Essential Medium (Flow Laboratories, Irvine, Calif). The same medium was also used for placebo.

The vaccine and placebo preparations were divided into 1-mL vials, which were numbered from 1 to 240 following a randomization list prepared by computer. The vials were kept frozen at -70° C. For vaccination, the number of vials needed for each day was thawed and stored on crushed ice until use.

The majority of infants were breast fed. The mothers were instructed not to feed the infants for 90 minutes before vaccination and 2 hours after vaccination. The vaccine was administered together with 30 mL of soy milk formula (Medisoija, Semper AB, Sweden). The vaccine (1 mL) was placed in the back of the mouth with a tuberculin syringe.

Clinical Follow-up

Clinical reactions were monitored at home for a period of 7 days after vaccination. The parents took daily rectal temperatures, kept a record of all stools passed by the baby, and recorded episodes of vomiting. They also observed the general condition of the infant and noted if unusual irritability or restlessness was present. A participating pediatrician was available for consultations, and, as febrile reactions were not uncommon (see "Results" section), several parents contacted the pediatrician. None of the reactions appeared severe enough for the infant to be seen in the clinic. The home-monitoring checklists were

returned 1 month later when the infant was seen for a postvaccination blood specimen.

The follow-up for diarrhea covered two Rotavirus winter seasons and lasted until the end of June 1987. During the follow-up, the parents received several reminders of the ongoing study. The parents were instructed to contact the study nurse if the infant had unusually loose stools (three or more unformed stools). In each such case, a stool specimen for Rotavirus studies was collected, and the parents began to keep a home checklist for symptoms on a similar form as used for the follow-up of vaccine reactions. All babies with any notable severity of symptoms were seen by a participating pediatrician in the outpatient clinic of the Tampere University Central Hospital. The treatment of diarrhea followed the general principles of oral rehydration and minimal interruption of feeding. If necessary, the infant was hospitalized for treatment.

Laboratory Specimens

Venous blood specimens were collected before vaccination and 1 month (±1 week) after vaccination. The serum samples were shipped frozen to the Laboratory of Infectious Disease, National Institutes of Health, for *Rotavirus* antibody studies. The serological tests were performed under code.

Laboratory Methods

Stool specimens were collected as early as possible during each episode of diarrhea. All the stool specimens were tested for *Rotavirus*, but other diarrheal pathogens were not systematically looked for. Nevertheless, stool specimens from 71 episodes (of 89 detected) were cultured for *Campylobacter*, *Salmonella*, and *Yersinia*, using standard methods. All cultures were negative.

The stool specimens were first screened for *Rotavirus* in Tampere using the Dakopatts (Glostrup, Denmark) enzyme-linked immunosorbent assay and the WHO kit for *Rotavirus* antigen, supplied by the WHO Collaborating Centre for Reference and Research on Rotavirus, Birmingham, England. Those found positive in the WHO en-

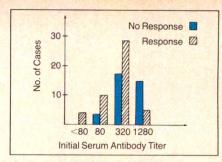


Fig 1.—Correlation between initial *Rotavirus* serotype 3 antibody titer and response to vaccination.

zyme-linked immunosorbent assay were retested using a WHO confirmatory test with a blocking antiserum. ¹⁵

The confirmed *Rotavirus*-positive stool specimens, of which a sufficient quantity were still available, were tested for *Rotavirus* serotypes at the WHO Collaborating Centre in Birmingham, using an enzymelinked immunosorbent assay method with appropriate monoclonal antibodies. ¹⁶ *Rotavirus* antibody studies were performed at the National Institutes of Health using plaque reduction neutralization assay ¹⁷ or tube neutralization assay ¹⁸; some serum samples were tested with both methods.

Clinical Rating of Diarrhea

A scoring system used in a trial of the RRV-1 vaccine in Venezuela was extended to a 0 to 20-point scale and applied to assess the clinical severity of cases of diarrhea. This score considered the following variables: duration of diarrhea (score 0 to 3), maximum number of stools per 24 hours (score 0 to 3), duration of vomiting (score 0 to 3), maximum number of vomiting episodes (score 0 to 3), degree of dehydration (score 0 to 3), maximum temperature (score 0 to 2), and need for hospitalization (score 0 or 3).

RESULTS

A total of 200 infants were vaccinated; 100 infants received the RRV-1 vaccine and 100 received placebo. A postvaccination blood specimen was obtained from 198 infants (99 in each group).

Rotavirus Antibody Responses

Most of the infants had *Rotavirus* antibody, presumably of maternal origin, at the time of vaccination. Evidence of seroconversion or fourfold or greater rise by one neutralization test or the other was found in 61 (62%) of the vaccinees and 3 (3%) of the placebo recipients (Table 1). The latter was apparently due to intercurrent natural *Rotavirus* infections, although none of the 3 infants experienced any clinical symptoms

[†]Twelve paired serum samples were tested with both methods.

within the month after vaccination. There was an apparent inverse correlation between the initial serum plaque reduction neutralization antibody level for rhesus *Rotavirus* vaccine and response to vaccination (Fig 1): infants with a low initial antibody level were more likely to respond than those with a high level of *Rotavirus* PRN antibody.

Clinical Reactions After Vaccination

Clinical reactions could be assessed in 98 RRV-1 vaccine recipients and 97 placebo recipients, from whom adequately filled symptom checklists were returned. Febrile reactions (temperature, ≥38.0°C), clustering around days 3 and 4 after vaccination, were seen following administration of the RRV-1 vaccine but not following administration of placebo (Fig 2). A total of 26 RRV-1 vaccinees (26%) had a rectal temperature over 38°C on either or both of those days; of these, 7 infants had a temperature over 39°C. None of the pla-

cebo recipients had a rectal temperature over 38°C on days 3 or 4 after vaccination, although a few had fever on some other days of follow-up.

Fever was commonly accompanied by unusual irritability and restlessness in the infant (Fig 2). However, such symptoms were not uncommon in the placebo recipients either (Fig 2). The excess of irritability in the vaccinees was statistically significant on day 4 after vaccination (P=.024, z test) but not on the other days of follow-up.

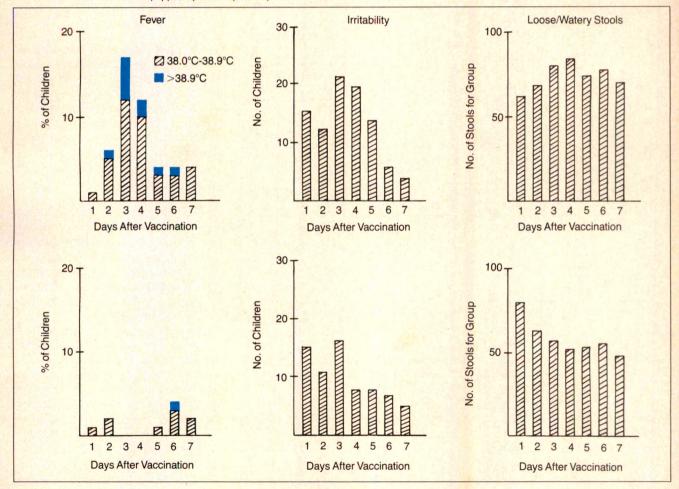
No frank diarrhea (\geq 3 loose stools per day) was seen in the vaccinees. However, there was an increase in the number of loose stools in the vaccine-treated group on day 3 after vaccination, whereas no such change was seen in the placebo-treated group (Fig 2). The mean number of loose or watery stools per infant on day 3 was 0.82 ± 0.92 in the vaccine-treated group and 0.60 ± 1.03 in the placebo-treated group (P=.119, t test); on day 4, the corresponding num-

bers were 0.84 ± 1.16 and 0.57 ± 0.87 (P = .04, t test).

Clinical Protection

A total of 89 episodes of diarrhea were recorded during the entire follow-up. Of these, 37 episodes were in the RRV-1 vaccine-treated group and 52 were in the placebo-treated group (P = .0166,z test). There were 26 cases of confirmed Rotavirus diarrhea; of these, 10 occurred in RRV-1 vaccine recipients and 16 in the placebo-treated group (P=.104, z test). Thirteen of the Rotavirus strains could be serotyped: 7 belonged to serotype 1 and 6 to serotype 4. The distribution of Rotavirus serotypes identified in the vaccine- and placebotreated groups is given in Table 2. There was no significant difference between the groups; ie, there was no evidence of preferential protection against either of the detected Rotavirus serotypes or against the Rotavirus of undefined serotype.

Fig 2.—Daily recordings of rectal temperature, unusual irritability, and loose/watery stools of recipients of the RRV-1 Rotavirus vaccine (top) and placebo (bottom) within 1 week after vaccination.



Rotavirus Serotype	Vaccine	Placebo	Statistical Significance
1	3	4	.352
4	2	4	.203
Not typed	5	8	.195
Total	10	16	.104

^{*}P value, z test.

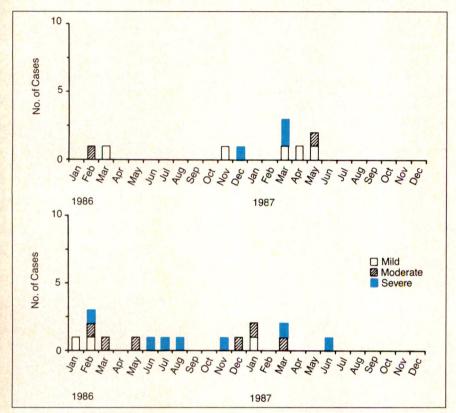


Fig 3.—Time and clinical severity of cases of *Rotavirus* diarrhea in the groups given RRV-1 vaccine (top) and placebo (bottom). Clinical rating of diarrhea was as follows: mild (score 1 to 4), moderate (score 5 to 8), and severe (score 9 and above).

		No. of	Cases
Severity	Score	Vaccine	Placebo
Mild	1-4	5	3
Moderate	5-8	2	7
Severe	≥9	3	6

^{*}In comparison of groups by Fisher's Exact Test, no difference was significant.

The timing and clinical severity of cases of *Rotavirus* diarrhea are presented in Fig 3. In the first 8 months of study from January through August 1986, there were two cases in the vaccine-treated group vs nine cases in the placebo-treated group (not significant). From November 1986 through June 1987 (second epidemic season), there were eight cases in the vaccine-treated

group and seven in the placebo-treated group (not significant). Thus, no clinical protection by the vaccine was seen in the second year of the study.

The clinical severity of *Rotavirus* diarrhea was assessed using a score described in the "Patients and Methods" section. The mean score in the RRV-1 vaccine–treated group was 6.1 ± 4.0 and in the placebo-treated group 7.5 ± 2.7

(not significant). Based on the same score, the cases were divided into mild, moderate, and severe (Fig 3 and Table 3). There were more severe and moderately severe cases in the placebotreated group, but the difference between groups was not statistically significant.

The cases of non-Rotavirus diarrhea were generally milder than those with Rotavirus. There were 27 non-Rotavirus cases in the vaccine-treated group and 36 in the placebo-treated group. Adequately filled symptom sheets were returned for 15 cases in the vaccine-treated group and 27 cases in the placebo-treated group. In these cases, the mean severity score was 4.7 ± 2.9 in the RRV-1 vaccine-treated group and 5.7 ± 2.9 in the placebo-treated group (not significant).

There was no apparent correlation between the serological response to RRV-1 vaccination and subsequent clinical protection. Of the 10 infants in the vaccine-treated group in whom *Rotavirus* diarrhea developed during the follow-up, 6 had originally shown a four-fold or greater rise in *Rotavirus* antibodies after vaccination.

COMMENT

The RRV-1 rhesus *Rotavirus* vaccine induced only partial protection against *Rotavirus* diarrhea; this was evident mainly in the first epidemic season following vaccination. The episodes of *Rotavirus* diarrhea on the average were slightly milder in the vaccinees than in the controls, indicating that the RRV-1 vaccination modified the clinical course of subsequent natural *Rotavirus* infection.

The performance of the RRV-1 vaccine in this study might be compared with results of (1) other trials of the same vaccine in different settings and (2) earlier trials of bovine *Rotavirus* vaccine in the same setting.

A trial of RRV-1 vaccine in young infants in Caracas indicated good protection against the homologous *Rotavirus* serotype (type 3), but protection against the other serotypes could not be measured because the numbers of other *Rotavirus* types were small. If n a study in Sweden, a higher dose (10⁵ PFU) of the RRV-1 vaccine, given to 5- to 12-month-old infants, induced a 48% protection rate against all diarrhea and 72% protection against diarrhea with a severity score of 6 or higher on a 0 to

20-point scale, associated primarily with serotype 1 *Rotavirus*. ¹⁹ In contrast, a trial in Rochester, NY, in a similar population as in the present study (2 to 5 months of age) and using the same vaccine dose (10⁴ PFU), indicated no protection against serotype 1 *Rotavirus* diarrhea. ²⁰

The accumulated experience suggests that important determinants of clinical protection following vaccination with rhesus Rotavirus vaccine might include serotype of challenge virus, vaccine dose given, and age at immunization. In the present study, only Rotavirus serotypes 1 and 4 were encountered, and, apparently, the protection was similar against both of these. More recently, human Rotavirus-rhesus Rotavirus reassortants have been constructed. These incorporate a single gene from a human Rotavirus, namely, that which encodes the major neutralization antigen (VP7) on the surface of the virus.21 Conceivably, such reassortant rotaviruses might induce better protective immunity against each of the human Rotavirus serotypes; this question will be assessed in the first clinical trials of the reassortant Rotavirus vaccines initiated recently.

Increase in vaccine dose could hardly be a practical way of improving the performance of the RRV-1 vaccine, since a higher inoculum is definitely associated with an increased rate of febrile reactions. Febrile reactions were previously detected in 64% of Finnish children 11 and 79% of Swedish children¹⁹ receiving 10⁵ PFU of the RRV-1 vaccine. The present dose, 104 PFU, induced a febrile reaction in 26% of the recipients, which is marginally acceptable, particularly as none of the infants were seriously ill. A similar rate of febrile reactions with the 104-PFU dose has been observed in the United States, 10,20 but febrile reactions were much less common in Venezuelan infants aged 1 to 10 months.22 A lower dose of the vaccine (103 PFU) has also been tried, but the immune responses have been inadequate.12 Therefore, the currently used vaccine dose appears to be most feasible.

The age at vaccination appears to correlate with vaccine-induced clinical protection in studies of both rhesus and bovine *Rotavirus* vaccines. In studies of the RRV-1 vaccine in Sweden, as in studies of RIT 4237 bovine *Rotavirus* vaccine in Finland, involving 5- to

infants. protection 12-month-old against all Rotavirus diarrhea was of the order of 50% and protection against severe diarrhea of the order of 80%. 2,3 In contrast, vaccination of newborn infants with bovine Rotavirus vaccine resulted in no reduction of Rotavirus diarrhea cases but in only a shift in clinical severity toward a milder course in the vaccinees.23 The protective efficacy of the RRV-1 vaccine in this trial of 2- to 5-month-old infants was between the previous experiences in older and younger infants.

The mechanism responsible for clinical protection after Rotavirus vaccination is unknown and may be different for the bovine and rhesus Rotavirus vaccines. Bovine Rotavirus is highly attenuated for humans, and high doses (108 PFU) of the virus have been used in clinical studies. This contrasts with the 104 PFU of rhesus Rotavirus used in this trial. Thus, the rhesus Rotavirus must depend on effective multiplication in the host to produce a sufficient quantity of new progeny virus for the induction of an immune response. It is known that RRV-1 vaccine induces a more vigorous antibody response than the RIT 4237. 11 but the significance of these antibodies in protection remains unclear. For example, in the present study, seroconversion after vaccination did not predict subsequent protection against Rotavirus diarrhea.

As long as the correlates of protective immunity against *Rotavirus* disease are unclear, clinical trials remain the only way of determining vaccine efficacy. While the rhesus *Rotavirus* vaccine itself may no longer appear as a serious candidate for human *Rotavirus* vaccine, its reassortants hold a greater promise. ^{4,21} In future testing of those vaccines, the experience of RRV-1 vaccination should be considered as an important comparison.

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Total Serum IgE Levels in Children With Pertussis

Donato Torre, MD; Marwan Issi, MD; Giovanni Chelazzi, MD; Giovanni Paolo Fiori, MD; Carmen Sampietro, MD

• Total serum IgE levels were evaluated in 20 children with pertussis. Increased levels of serum IgE were observed in the group of children between the ages of 3 and 12 years, while normal levels of serum IgE were detected in the groups of children between birth and 24 months old and between 13 and 24 months old. A further and significant increment of serum IgE levels was also found after 10 days of hospitalization.

(AJDC. 1990;144:290-291)

Bordetella pertussis has well-established immunologic adjuvant activity. In 1958, Mota1 showed that administration of whole B pertussis organisms to rats caused a striking adjuvant effect for antibody production, especially IgE. The B pertussis organism also causes a rise in IgE antibody in guinea pigs² and in mice. The adjuvant effect is produced by at least two distinct substances in B pertussis cells: heat-stable endotoxin or lipopolysaccharide4 and a heat-labile protein, pertussis toxin.5 Tada et al6 showed that purified pertussis toxin stimulated IgE production when it was given concurrently with an injection of egg albumin. Arai and Munoz showed that pertussis toxin given intravenously together with hen's-egg albumin increased the IgE antibody response. In addition, the same authors demonstrated that small doses (0.1 ng) of pertussis toxin stimulated the IgE response to egg albumin.8 An IgE response to the components of B pertussis, such as pertussis toxin, filamentous hemagglutinin, and agglutinogens, may be an important defense mechanism for *B* pertussis in the respiratory tract. Haus et al⁹ demonstrated specific IgE antibodies to *B* pertussis antigen in infants after vaccination.

We evaluated total serum levels of IgE in children with pertussis and demonstrated normal levels in young children and elevated levels in older children. We speculate on the possible mechanisms for IgE production in older children with pertussis.

PATIENTS AND METHODS

Twenty children (12 boys and 8 girls) affected by pertussis were admitted to the Division of Infectious Diseases, Regional Hospital, Varese, Italy, between January 1987 and October 1988. Their mean age was 3.5 years (range, 2 months to 11 years). None had a history of allergic diseases, prior infection with pertussis, or immunization with pertussis vaccine. All patients had intense and/or severe paroxysmal attacks of whooping cough; several patients had episodes of apnea. Most patients showed a typical leukocytosis with a predominant lymphocytosis. In all patients, the diagnosis was based on isolation of B pertussis from Bordet-Gengou medium and/or by direct examination of respiratory secretions by fluorescent antibody technique. Forty healthy children matched for sex and age served as the control group.

Blood samples were obtained from all patients on admission to the hospital and from several patients after 10 and 15 days of hospitalization. The sera were separated within 24 hours of collection, and they were frozen and stored at -20° C until assayed. Total serum

IgE levels were determined by a solid-phase immunoenzymatic method. All samples were analyzed in duplicate.

Data are expressed as mean (\pm SD). The Mann-Whitney U test for unpaired data was used to assess differences between patients with pertussis and controls. Analysis of variance on log-transformed data was used to study changes of serum IgE levels over time. For all assessments, the null hypothesis was rejected if the P < .05.

RESULTS

Table 1 displays IgE levels in relation to patient age. Normal levels of serum IgE were found in the group of children between birth and 24 months old. Two of 14 children from this group had high levels of serum IgE. In the group of children between 3 and 12 years old, a significant increase of serum IgE levels was detected (P < .01). The IgE levels during the course of the disease in the group of children 3 to 12 years old are listed in Table 2. Persistent and increased levels of IgE were observed during the course of disease. After 10 days of hospitalization, IgE levels were higher than those on admission (P < .05), notwithstanding antibiotic treatment and supportive therapy.

COMMENT

Normal levels of IgE were found in the group of younger children with pertussis, while in the group of older children, a higher level of IgE was

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Table 1.—Total Serum IgE Levels (Mean ± SD) According to Age of 20 Patients With Pertussis				
lgE, µg/L				
Subjects	0-12 mo	13-24 mo	3-12 y	
Controls (n) Patients with	38.8 ± 21.1 (12)	86.4±61.4 (13)	168.0 ± 45.6 (15)	
pertussis (n)	91.4 ± 146.1*(8)	164.1 ± 217.2*(6)	698.4 ± 436.5†(6)	

*Not statistically significant

†P<.01 when compared with the control group.

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Table 2.—Total Serum IgE Levels During the Course of Disease in 6 Older Patients With Pertussis

			lgE, μg/L at Day		
Patient	Age, y	Severity of Disease*	0	10	15
1	4	8	302.4	367.2	400.8
2	6	8	1084.8	2049.6	840.0
3	6	7	924.0	1008.0	420.0
4	11	4	290.4	1044.0	684.0
5	9	3	1248.0	2328.0	916.8
6	8	4	340.8	1406.4	904.8
Mean ± SD	7.3±2.5		698.4 ± 436.5	1367.0 ± 724.3†	694.3 ± 234.9

^{*}Score of severity of disease is as follows: 0-2, intense whooping attacks with gradual and complete resolution; 3-5, severe and persistent whooping attacks with a slow and complete resolution; and 6-8, severe whooping attacks with episodes of apnea and incomplete resolution.

†P<.05 when compared with the values on admission.

observed. Using enzyme-linked immunosorbent assay, Finger and Wirsing von Koenig10 detected IgE antibodies to whole-cell preparations of B pertussis in only 4 of 142 children with pertussis. All children of this study were 3 months to 4 years old. To our knowledge, no assessment of total serum IgE levels in patients with pertussis has been done. The presence of normal total serum levels of IgE (in our study) as well as of specific IgE (in Finger and Wirsing von Koenig's study) in younger children could represent a peculiar aspect of Bordetella infection. Although a specific IgE antibody against B pertussis has been described following vaccination,9 the lack of enhanced IgE activity in younger children with naturally acquired pertussis infection may be related to physiologic immune depression (especially in the first 6 months of life) together with depression of cell-mediated immune response induced by B pertussis infection.11 In addition, younger children tend to shed more organisms and for longer periods, sometimes for up to 2 to 3 months (if untreated). This phenomenon may reflect a slower immune response than that of older children as measured by the rise of serum antibodies. ¹² In our study, enhanced IgE activity was observed only in older patients.

A component of B pertussis, pertussis toxin, appears to be responsible for the stimulation of IgE antibodies. Ishizaka et al¹³ have shown that pertussis toxin stimulated a population of normal T cells to release a glycosylation-enhancing factor. This factor introduced an N-linked oligosaccharide to IgEbinding factors that converted the IgEbinding factors into enhancers of IgE synthesis. However, other theories suggest that increased IgE response occurs by decreasing suppressor T lymphocytes or by increasing helper T cells. 6,14 Our data do not shed light on the actual mechanism.

CONCLUSION

The strong interaction of pertussis toxin with IgE is of interest because pertussis toxin is known to be an adjuvant that elicits an IgE response. Whether this interaction contributes to

the adjuvant effect remains to be elucidated, especially in younger children who did not show an IgE response to infection with *B pertussis*.

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Protective Efficacy of *Haemophilus influenzae* Type b Polysaccharide-Diphtheria Toxoid-Conjugate Vaccine

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 We estimated the relative protective efficacy of Haemophilus influenzae type b polysaccharide (PRP) vaccine and PRPdiphtheria toxoid-conjugate (PRP-D) vaccine using data from reports of cases of invasive Haemophilus disease occurring in vaccinated children submitted to the Food and Drug Administration, Rockville, Md, and Washington University, St Louis, Mo. During the first 13 months following licensure of each of the vaccines, there were 127 cases reported in recipients of PRP vaccine vs 17 cases in recipients of PRP-D vaccine. The total number of reported cases for each vaccine is not necessarily comparable, since the extent of vaccine use in the population and the extent of reporting of cases may have been different during the two periods. However, the proportion of reported cases occurring equal to or 14 days or more after vaccination (a period considered sufficient to develop immunity) was significantly greater for PRP vaccine (106 [83%] of 127 cases) compared with PRP-D vaccine (7 [41%] of 17 cases). Based on the ratio of late-onset to early-onset cases observed for PRP vaccine, we would have expected 50 late-onset cases after PRP-D vaccination. Since only 7 late-onset PRP-D vaccine failures were reported (86% fewer than expected), the data suggest that PRP-D vaccine was more effective in preventing disease 14 days or more after vaccination than was PRP vaccine.

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The Haemophilus influenzae type b polysaccharide-diphtheria toxoid conjugate vaccine (Prohibit; also referred to as PRP-D) was approved by the US Food and Drug Administration (FDA), Rockville, Md, in December 1987 and was recommended for use in children 18 to 59 months of age. 1,2 The vaccine is more immunogenic in children of all ages than the unconjugated H influenzae type b polysaccharide (PRP) vaccine, which was licensed in April 1985 primarily for children 24 to 59 months old.3 At the time the PRP-D conjugate vaccine was approved there was considerable controversy surrounding the issue of PRP vaccine efficacy in the United States. 46 Case-control studies conducted in various regions of the country yielded disparate efficacy estimates, ranging from -55% efficacy in Minnesota to +88% efficacy in a multicenter study in Connecticut, Dallas County, Texas, and Pittsburgh, Pa. 7-10 Consequently, there was great interest in how efficacious the new conjugate vaccine would prove, particularly since it was targeted primarily for 18-month-old children rather than 24-month-old children. The younger children are both at increased risk for disease11 and are potentially more difficult to immunize successfully than 24-month-old children.³

Vaccination with PRP-D was associated with a protective efficacy of 87% in Finnish children immunized at 3, 4, and 6 months of age, ¹² but it had no significant protective efficacy in Native Alaskan infants immunized at 2, 4, and 6 months of age. ¹³ To our knowledge, there presently are no published data available on the efficacy of PRP-D vaccine in other US populations. It is generally agreed that a randomized, double-blind, placebo-controlled clinical trial is the optimal way to assess vaccine efficacy. ¹⁴ However, once a vaccine is

licensed it is, under most circumstances, unethical to conduct such trials. Alternative approaches, such as case-control and retrospective cohort studies, ¹⁴⁻¹⁶ are therefore needed.

In this report we propose an alternative approach to estimating the relative efficacy of two vaccines using spontaneous reports of cases of invasive H influenzae type b disease occurring in vaccinated children. Traditionally, spontaneous reports have provided only limited information about vaccine efficacy, because it has not been possible to determine the proportion of total cases they represent, and because the extent of vaccination in the population has not been known. However, since vaccination with H influenzae polysaccharide vaccine17,18 and other polysaccharide vaccines19-21 is not expected to confer protection against disease for at least 1 week, we reasoned that disease occurring during this period (ie, "early-onset" cases) would reflect background rates of disease. In contrast, although the minimal interval required to mount protective immune responses to PRP or PRP-D vaccine is not known with certainty, 17,22 cases occurring 14 days or more after vaccination (ie, "late-onset" disease) probably represent "true" vaccine failures. Therefore, it is possible to estimate the relative efficacy of the two vaccines by comparing the respective ratios of late-onset to early-onset cases. That is, if two vaccines are equally ineffective in preventing disease in the first week after vaccination but equally effective in preventing late-onset disease, we would expect that the respective ratios of late-onset to early-onset cases for each of the vaccines would not be significantly different.

METHODS

We reviewed all reports of invasive H influenzae type b disease occurring in

children previously immunized with PRP or PRP-D vaccine that were submitted to the FDA Spontaneous Reporting System or to investigators at Washington University School of Medicine, St Louis, Mo. The FDA Spontaneous Reporting System is a computerized database that contains spontaneous reports of adverse drug experiences submitted by pharmaceutical manufacturers and health professionals.^{23,24} As previously described,^{25,26} the Washington University cases were identified from spontaneous reports from physicians and through active surveillance for Hinfluenzae disease in Minnesota, Dallas County, Greater Pittsburgh, and Connecticut.10 In addition, cases detected by active surveillance by the Kaiser Permanente Medical Groups Inc in northern California9 and in southern California27 were reported to the FDA. In Minnesota, Dallas, and northern California, prospective active surveillance was in place for the entire study. However, in Pittsburgh and Connecticut, prospective active surveillance began 9 months after licensure of PRP, and in southern California, active surveillance began 3 months after licensure of PRP-D.27

A case was defined as a clinical illness in a child previously immunized with PRP or PRP-D vaccine that was associated with isolation of H influenzae from normally sterile body sites, such as cerebrospinal fluid, blood, or joint fluid. Since type b polysaccharide antigen may be excreted in urine for up to 11 days following PRP immunization,28 detection of antigenuria is not useful for confirming cases occurring shortly after vaccination. Therefore, to maintain consistency in the diagnosis of early-onset and late-onset disease, only culture-proved cases were included. Six children who developed disease more than 14 days after PRP vaccination and had antigen detected in serum (n = 1) or urine (n=5) were excluded because of lack of culture confirmation (three children with pneumonia and one child each with facial cellulitis, arthritis, and epiglottitis). No potential cases associated with PRP-D vaccine were excluded.

The study period encompassed the first 13 months following licensure of each of the vaccines. For PRP vaccine, the study period was April 12, 1985, through May 11, 1986, and for PRP-D vaccine the study period was December 22, 1987, through January 21, 1989. Children who were vaccinated during these 13-month periods but who developed disease beyond these intervals were excluded from the analysis. Because the interval required to generate a protective immune response to vaccination is not known with certainty but probably ranges from 7 to 14 days, 17,22 it was decided at the outset of the study to exclude cases occurring during the second week following immunization, since it

Table 1.—Distribution of Cases of Invasive Haemophilus influenzae Disease by Vaccine and Interval to Onset of Disease

	Vaccination	al From on to Onset ease, d*	Ratio of Late-Onset to
Vaccine	≤7	≥14	Early-Onset Cases
PRP-D,† No. of cases	10	7‡	0.7
PRP, No. of cases	21	106‡	5.0

*One case was reported to have onset of disease between 8 and 13 days following immunization with *H* influenzae type b polysaccharide (PRP) vaccine and was excluded (see "Methods" section).

†PRP-D indicates PRP-diphtheria toxoid-conjugate.

‡P<.001 by Fisher's Exact Test.

would not be possible to assess whether they represented background cases of disease or vaccine failure. Cases were thus classified according to whether disease occurred within 7 days or at least 14 days following immunization. Interestingly, only one case, a child with onset 13 days following PRP vaccine, was reported to have occurred between 8 and 13 days following immunization with either vaccine.

Fisher's Exact Test was used to test for an association between vaccine type and interval to disease. A standard test for the comparison of two proportions was used to compare proportions.²⁹

RESULTS

There were 127 cases of invasive H influenzae disease associated with PRP vaccination and 17 cases associated with PRP-D vaccination during the respective first 13 months following licensure of each of the vaccines. Sixteen of the 127 PRP cases occurred in children residing in geographic areas with active surveillance compared with 4 of the 17 PRP-D cases (P>.4 by Fisher's Exact Test). The 111 spontaneous reports of cases occurring after PRP vaccination came from 31 states and the District of Columbia, and the 13 spontaneous reports of cases occurring after PRP-D vaccination came from 12 states and British Columbia.

Table 1 presents the distribution of cases by interval from vaccination to onset of illness and by type of vaccine. The proportion of cases occurring 14 days or more after PRP vaccination was 106 (83%) of 127. In contrast, the proportion of cases occurring 14 days or more after PRP-D vaccination was significantly smaller (7 [41%] of 17, P<.001). For PRP and PRP-D vaccines, the respective ratios of late-onset to early-onset cases were 5.0 and 0.7. Based on the ratio of late-onset to early-

onset cases observed for PRP vaccine, if the efficacy of the two vaccines were equal, we would have expected 50 lateonset cases following PRP-D vaccination. Instead, only 7 late-onset PRP-D vaccine failures were reported, 86% fewer than expected.

Analysis of the cases reported from areas with active surveillance was limited by the small number of cases. For all of the active surveillance areas, except Kaiser Permanente in northern California, there were a total of one early-onset and nine late-onset cases after PRP vaccine, and two early-onset and one lateonset case after PRP-D vaccine. These distributions are consistent with those observed in the spontaneous reports from the rest of the country. However, active surveillance conducted by Kaiser Permanente in northern California identified four early-onset and two lateonset cases after PRP vaccine, a distribution different from that observed in the other active surveillance areas (P=.03 by Fisher's Exact Test). The corresponding numbers of early-onset and late-onset PRP-D cases identified by surveillance in northern California were 0 and 1. Thus, the four early-onset cases observed after PRP vaccine in northern California appear to be an unusual cluster, an inference reinforced by the fact that no subsequent early-onset cases following PRP or PRP-D vaccination were observed in that surveillance area as of April 1989 (S. Black, MD, oral communication). A similar cluster of early-onset cases after PRP vaccine was observed in Minnesota in the second year after licensure of PRP vaccine, but only one subsequent earlyonset case (after PRP-D vaccine) has been observed in Minnesota as of December 1989 (M. T. Osterholm, PhD, MPH, oral communication).

Table 2.—Characteristics of Cases of Invasive Haemophilus influenzae Disease Occurring After H influenzae Type b Polysaccharide (PRP) or PRP-Diphtheria Toxoid-Conjugate (PRP-D) Vaccination

		Patien	t Group	
	Onset ≤7 d*		Onset ≥14 d*	
Variable	PRP (n = 21)	PRP-D (n = 10)	PRP (n = 106)	PRP-D (n=7)
Disease, No. (%) of subjects Meningitis	6 (29)	7 (70)	63 (59)	7 (100)
Epiglottitis	6 (29)	0	25 (24)	0
Other†	9 (43)	3 (30)	18 (17)	0
Male, No. (%) of subjects	8 (38)	5 (50)	66 (62)	3 (43)
Median age at vaccination, mo (range)	30 (18-41)	22.5 (18-32)	25 (18-58)	18 (18-20)
Median interval from vaccination to onset of disease, d (range)	3 (1-7)	3 (1-6)	90 (14-290)	50 (14-174)

^{*}The interval is from vaccination to onset of disease.

Selected characteristics of the earlyonset and late-onset cases analyzed in the present study are summarized in Table 2. Of note, no cases of epiglottitis were reported in association with PRP-D vaccine.

COMMENT

The exact efficacy of PRP vaccine remains controversial.46 Published estimates range from no efficacy to rates of 50% to 88%. 8-10 It should be emphasized that our data do not permit a direct determination of the actual protective efficacy of either PRP or PRP-D vaccine. However, whatever the actual efficacy of PRP vaccine, the finding that the proportion of cases occurring 14 days or more after PRP-D immunization was significantly smaller than the proportion of cases occurring 14 days or more after PRP immunization suggests that PRP-D vaccine was more effective than the PRP vaccine in preventing invasive Hinfluenzae type b disease.

In interpreting this finding, it is important to consider the assumptions and potential biases underlying our analysis. First, we assumed that neither vaccine conferred protection against disease during the first 7 days following vaccination and, consequently, that disease observed during this interval reflected background rates of disease. Some investigators have proposed that PRP vaccine may actually increase the risk of disease during the first week following vaccination, 47.9 possibly as a

result of a transient decline in serum anticapsular antibody. 17,30 If vaccination with PRP but not PRP-D increases the risk of disease in the first 7 days, then cases associated with PRP vaccine would be the sum of "background" cases plus cases resulting from the increased risk. In contrast, cases associated with PRP-D vaccine in the 7 days after vaccination would represent only background cases. However, by including early-onset PRP vaccine cases other than background cases in calculating the ratio of late-onset to early-onset cases, we would have underestimated the "true" ratio of late-onset to earlyonset cases for PRP vaccine and thereby underestimated the relative efficacy of PRP-D vaccine. Note also that during the first few days after PRP or PRP-D vaccination, similar patterns of antibody decline are observed. 17,22 This finding suggests that if there is a transient increase in the risk of disease after vaccination, it may be comparable for both vaccines.

A second assumption concerned the relative comparability of reporting of late-onset and early-onset cases for children vaccinated with PRP or PRP-D vaccines. We compared the first 13 months following licensure of each vaccine rather than the same 13-month period, because studies have shown that adverse drug experience reporting is affected by the length of time a product has been marketed, with the largest number of reports received in the early

years of marketing. Nevertheless, our results could be explained by a bias toward either overreporting early-onset PRP-D cases (relative to reporting of early-onset PRP cases) or underreporting late-onset PRP-D cases. We believe a bias toward relative overreporting of early-onset PRP-D cases is an unlikely explanation for our results. Invasive H influenzae type b disease occurring within a few days after vaccination with either vaccine is notable, and it seems unlikely that reporting patterns would be very different for the two vaccines. However, we cannot exclude the possibility that adverse publicity regarding PRP vaccine in the period preceding PRP-D licensure might have led to an increase in reporting of early-onset PRP-D cases during the first 13 months after its licensure.

With respect to a possible bias toward underreporting of late-onset PRP-D cases compared with PRP cases, note that only seven late-onset PRP-D cases were reported during the first 13 months after licensure of PRP-D. 86% fewer than expected based on the ratio of late-onset to early-onset PRP cases (Table 1). Although this small number might reflect underreporting, we believe that this possibility is also unlikely. First, considerable attention in the news media and medical literature had been given to the question of H influenzae type b vaccine efficacy in the period after licensure of PRP-D,5,6 and this publicity would have been expected to increase reporting of PRP-D vaccine failures. Second, by the time of licensure of PRP-D vaccine, active surveillance of Haemophilus disease had been extended from Minnesota, Dallas County, and Kaiser Permanente in northern California9 to include also Greater Pittsburgh, Connecticut, 10 and, beginning April 1, 1988, the Kaiser Permanente group in southern California.27 Thus, this increase in size of the population under active surveillance should have resulted in an increase in ascertainment of PRP-D cases.

Finally, we cannot exclude the possibility that PRP vaccine was used more widely during the first months after its licensure compared with the use of PRP-D in the first months after its licensure. More extensive use of PRP during the initial months of marketing

t"Other" includes pneumonia, septic arthritis, cellulitis, and bacteremia.

would have created relatively more person-months of follow-up time for lateonset PRP cases to have occurred than for PRP-D. To allow for this possibility. we reanalyzed our data to include reports of PRP-D vaccine failures that occurred during the 6 months after January 21, 1989, the end of the initial 13-month study period. The results remained essentially unchanged: for the 19 months of PRP-D vaccine marketing. the ratio of late-onset to early-onset cases was 11:12. Therefore, even if there were differences in the relative use of the two vaccines in the immediate periods after marketing, these differences did account for the difference observed in the respective ratios of lateonset to early-onset cases.

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In summary, we recognize that spontaneous reporting of vaccine failure is subject to numerous known and unknown bias, and, therefore, one must be cautious in drawing inferences from the reported events. However, we believe that the large difference in the ratios of late-onset to early-onset cases between the two vaccines is unlikely to have resulted from chance alone or from biased reporting. Therefore, our observations are consistent with greater protective efficacy of PRP-D vaccine than PRP vaccine in preventing invasive H influenzae disease 14 or more days following vaccination. This conclusion is noteworthy because the PRP-D vaccine was recommended for 18-month-old children, a population at higher risk of disease than the 24-month-old and older children who were the principal recipients of PRP vaccine.

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Immunity to Measles in a Large Population of Varying Age

Significance With Respect to Vaccination

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 During a measles outbreak, 660 hospital employees of widely varying ages were screened for immunity to the disease using an automated indirect fluorescent antibody technique. Of these 660 employees, 623 indicated their year of birth; 21 were seronegative and 13 had borderline titers. Of those born before 1957, 7 tested seronegative and 6 were borderline, while 12 of those born between 1959 and 1964 were seronegative and 3 were borderline. There are several possible reasons for these findings. It is concluded that mass immunization of high-risk populations during outbreaks, while effective, is difficult to justify scientifically because only a small percentage of subjects are not immune. If facilities permit, mass screening during outbreaks may be feasible. Preferably, continuous screening and vaccination of susceptible high-risk employees could be performed. Our study also does not validate exclusion from immunization programs those born prior to 1957 in view of the fact that both seronegativity and disease occur in this age group with significant frequency.

(AJDC. 1990;144:296-298)

In late 1988 and the first half of 1989, there was an outbreak of measles in southern California, including San Bernardino County. In June 1989, a number of inmates of the county jail contracted measles. One prisoner was the victim of a particularly virulent, eventually fatal, episode requiring hospitalization at San Bernardino County Medical Center. Although initially there was no great concern about the possibility of the disease spreading, when a particularly severe episode of measles affected a member of the house staff and several other health care personnel, a condition approaching

panic gripped the hospital. Hospital authorities sought advice from public health and infectious disease experts and were told that mass immunization was recommended but that individuals born prior to 1957 need not be immunized and should be presumed to be immune.

Prompted by reports in the medical literature indicating that 90% or more of such populations were already immune and that there was significant morbidity among vaccinated individuals, we decided to offer immunity screening as an alternative option to those employees desiring to undergo such testing. We were able to carry out this screening because of the availability in our laboratory of an instrument (FIAX, Whittaker Bioproducts, Walkersville, Md) capable of automated indirect fluorescent antibody (IFA) immunologic testing.

SUBJECTS AND METHODS

Among medical center employees, a little more than 300 elected to be immunized without testing and 660 elected to be screened for immunity by IFA. All samples were obtained and studied during the last week in June and the first week of July 1989. Blood samples were taken from approximately 500 of these employees, testing was performed, and results were transmitted within the first 5 days after availability of testing was announced. The remainder of the participants straggled in and testing was completed in the following 10-day period. Serum samples from each of the 660 participants were tested in the FIAX system, which employs a two-sided solid phase reactor surface, one side of which is coated with inactivated measles antigen while the other side contains no antigen and serves as a blank. After immersion of the reactor in a 1:50 dilution of the serum of each patient to permit binding of IgG measles antibodies to the surface, the reactor with bound serum is washed and stained with fluorescein isothiocyanate-conjugated anti-human IgG. Following an additional wash, the reactor is placed in a specially designed fluorometer that quantitates the staining on the antigen-coated side and expresses it in fluorescence signal units (FSU) by comparison with the blank side (Δ FSU), to compensate for possible nonspecific binding. Supplied with the instrument is a computer program on cassette tapes that, on insertion into a microcomputer, automatically plots a calibration curve and computes the titer of each sample, printing these out sequentially on a paper tape.

Including clerical work and preparation, testing in batches of 100 or more consumes approximately 4 minutes per test; the actual testing of the sample and the printout take less than 10 seconds per test. With this test system, a titer of less than 8 FSU is considered seronegative (ie, nonimmune). Values between 8 and 12 FSU are considered borderline; all such samples were retested and reclassified on the basis of retest if the second result indicated a titer in excess of 12 FSU or below 8 FSU. Titers in excess of 12 FSU are considered to be immune (or positive for IgG antibodies) and were reported as such.

Because of the urgency of the testing, no information concerning previous immunization was solicited. All participants were told that they would be notified promptly if they were shown to be seronegative; vaccination was to be recommended and offered to such employees. Borderline titers were reported, but they were considered to represent immunity. All seronegative individuals who participated in the survey were monitored for the development of measles and were studied by serologic testing if clinically suspicious manifestations appeared; all others were instructed to report to the employee health service any illness that was suspicious for measles. All employees in whom the disease had developed prior to the survey had serologic studies of acute and convalescent serum samples to document that they had had measles.

RESULTS

The age distribution of participants and the results of immunity testing are enumerated in detail in Table 1. Table 2

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contains a further breakdown of some of the statistical data that may convey useful information to any organization facing a similar problem. Of the 660 employees screened, 623 indicated their year of birth. Of the 660 employees, 21 (3.2%) were seronegative, while 13 (2.0%) continued to have borderline values on retesting. There were 341 individuals who listed their dates of birth as before 1957. Of these, 7 (2.1%) tested seronegative, and 6 (1.8%) tested borderline. The difference in prevalence between these two groups is statistically significant (P < .05); the difference in prevalence is 2.9 times the SE of the difference. Put another way, one third of the seronegative group and almost half of the borderline group were born prior to 1957. Of the 282 subjects born in or after 1957, 14 (5.0%) were seronegative and 7 (2.5%) tested borderline. Twelve of the seronegative employees with a year of birth in or after 1957 were born during the 6-year period between 1959 and 1964. Twelve of the 14 seronegative values and 3 of the 7 borderline values were obtained from the 171 individuals born in those years, with incidences of 7.0% and 1.8%, respectively. When those born in that 6-year period are subtracted from the 282 individuals born in or later than 1957, 111 remained. Of these 111 employees, 4 (3.6%) tested borderline and 2 (1.8%) tested seronegative (Table 2).

The employees screened for immunity status, as well as those with apparent measles prior to the survey, were followed up, with the results listed as follows: (1) Two seronegative employees included in the survey, 1 born in 1941, had development of clinically characteristic measles, proved by seroconversion, within a few days after phlebotomy. (2) Of the 21 seronegative subjects included in the survey, 16 subsequently were vaccinated. Two had measles develop before they could be vaccinated; 2 could not be vaccinated because they were pregnant, and 1 refused vaccination. (3) The 3 employees who had been hospitalized with probable measles prior to the survey were proved to have the disease by seroconversion. One of these 3 was born in 1949, and another was born in 1953. (4) There were no other documented cases of measles among our employees.

Table 1.—Results of Immunity Testing for Measles by Year of Birth						
Years	No. Tested	No. Borderline Twice (%)	No. Not Immune	% Not Immune		
<1949	174	4 (2.3)	4	2.3		
1950	15	0	0	0		
1951	21	0	0	0		
1952	26	1 (4.0)	1	4.0		
1953	20	1 (5.3)	0	0		
1954	33	0	1	3.0		
1955	22	0	0	0		
1956	30	0	1	3.4		
Total <1957	341	6 (1.8)	7	2.1		
1957	26	1 (3.8)	0	0		
1958	40	0	0	0		
1959	36	1 (2.8)	2	5.6		
1960	35	1 (2.9)	2	5.7		
1961	32	0	1	3.1		
1962	22	0	2	9.1		
1963	33	1 (3.0)	4	12.1		
1964	13	0	1	7.7		
1965	8	1 (12.5)	0	0		
1966	13	1 (7.7)	0	0		
1967	7	1 (14.3)	0	0		
1968	5	0	0	0		
1969	10	0	2	20.0		
1970	1	0	0	0		
1971 Total Known Year of	1	0	0	0		
Birth	623	13 (2.1)	21	3.5		
Age not stated	37	0	0	0		
Grand Total	660	13 (2.0)	21	3.2		

Group*	Result	No. (%)
Born before 1957 (N = 341)	Not immune	7 (2.1)
	Borderline	6 (1.8)
Born in 1957 and later (N = 282)	Not immune	14 (5.0)
	Borderline	7 (2.5)
Born in 1959 through 1964 (N = 171)	Not immune	12 (7.0)
	Borderline	3 (1.8)
Born in 1957 or later but not in 1959 through 1964 (N = 111)	Not immune	2 (1.8)
	Borderline	4 (3.6)

^{*}Numbers in parentheses are the number tested.

COMMENT

In recent years, detection of antibodies to measles in the clinical laboratory has generally employed one of four methods: hemagglutination inhibition (HI), enzyme immunoassay (EIA), complement fixation (CF), or IFA. 3-8 Diagnosis of acute measles is usually achieved by demonstration of a rising titer of IgG class antibodies in serial

samples of serum. For this purpose, any of these methods can be employed efficaciously. ^{5,6} For determination of immune status, most studies in the past relied on HI testing, which is highly specific. ² Recently, several studies have shown that EIA is superior because of its greater sensitivity. ^{8,4,7} We and others have used FIAX IFA testing successfully for some time in the determination of immunity status for rubella

with comparable results to HI. The FIAX test for measles has become available only recently; the antigen used is the same as that incorporated into the most widely used EIA method3,7 (W. L. Boteler, MS, oral communication, July 1989). The FIAX IFA measles procedure has a specificity of 100% and a sensitivity of 97.7% when compared with EIA7 (W. L. Boteler, MS, oral communication, July 1989). In common with EIA and HI, there is, therefore, reasonable certainty that an individual who tests seropositive using FIAX is immune while testing seronegative using FIAX is an excellent but slightly less reliable index of susceptibi-

Statistical data on prevalence of seronegativity to measles of older individuals are difficult to obtain because since the measles vaccine became available, most studies have related to large outbreaks that occurred among young adults of school age and those of similar age in the military services. 2,3,9,10 Simultaneously, the maximum incidence has shifted to older children and young adults. 11 Unfortunately, history of disease or immunization has proved relatively unreliable in the assessment of both immunity and susceptibility.2,12 A recent serologic study of 148 health care workers in Dayton, Ohio, found that 4.3% of those born in or prior to 1957 and 10.2% of those born thereafter were seronegative; no further details were reported.13 In one study of 506 young adults during a school outbreak in 1977, 9% of individuals studied were demonstrated to be seronegative by HI.2 In that publication, the cited ages of those surveyed indicate that a large proportion of the students were born in 1959, one of the years of highest prevalence of seronegativity in our population. One might speculate that the use of killed virus vaccine between 1963 and 196714,15 and too early immunization with live virus vaccine 15,16 may have resulted in an increase of immunization failure among those who were young children during that period. This could possibly account for the higher prevalence of seronegativity in those born between 1959 and 1964.

Current Centers for Disease Control (Atlanta, Ga) recommendations do not call for vaccination of individuals born before 1957.1 Based on our survey, this would have resulted in failure to immunize one third of the susceptible population. It is not surprising that there was a statistically significant difference in prevalence of seronegativity between younger and older age groups, but this appears less important than the significant prevalence of both seronegativity and disease in older persons; three of the five hospital employees (as well as several jail inmates) who contracted measles were born before 1957. Trivial disease was not characteristic of this measles outbreak in San Bernardino County. There were four recorded fatalities (all of them jail associated) in our hospital alone. Four of the five hospital employees with measles required hospitalization. Under the circumstances, one must question the validity of the recommendation that those born before 1957 need not be immunized.

The recommendations that high-risk individuals be vaccinated rather than screened for immunity status during measles outbreaks is predicated on the assumption that testing is expensive and time-consuming and prevalence of seronegativity is relatively high. 13 Our experience suggests that these assumptions are not universally valid. Only about 3% of our tested employees proved to be seronegative. Testing by the method we used was neither timeconsuming nor expensive. The entire process, including transmission of results, was completed within 5 days for approximately 500 employees who requested early testing. Excluding overhead and equipment, but including all labor and phlebotomy costs, our expenditures were approximately \$4 per test; each dose of vaccine cost the hospital \$7.41. Our medical center, of course, has a large microbiology/immunology laboratory section, employing 11 licensed medical technologists, as well as an instrument that is highly efficient for mass screening. It is recognized that many health care facilities do not possess the resources to carry out such a survey; for those that do, immunity screening during an outbreak merits serious consideration. The efficacy of serologic testing in our center during the outbreak was documented by the fact that 16 of the 17 seronegative employees who required vaccination were immunized and more than 600 were saved the necessity of vaccination. Furthermore, no preventable cases of measles were recorded among our employees following the initiation of the program. All health care institutions might benefit from an ongoing serologic screening and immunization program for measles among employees, obviating the need for mass testing or vaccination during an outbreak.

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Please see brief summary of Prescribing Information on adjacent page.



REFERENCES:

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SUPRAX® cefixime/Lederle

see package insert for full Prescribing Information INDICATIONS AND USAGE

Otitis Media caused by Haemophilus influenzae (beta-lactamase positive and negative strains), Moraxella (Branhamella) catarrhalis (most of which are beta-lactamase positive), and Streptococcus

Note: For information on otitis media caused by Streptococcus pneumoniae, see CLINICAL STUDIES section.

Acute Bronchitis and Acute Exacerbations of Chronic Bronchitis caused by S pneumoniae and H influenzae (beta-lactamase positive and negative strains).

Perform culture and susceptibility studies to determine causative organism and its susceptibility to

SUPRAX. Therapy may begin while waiting for study results and may be adjusted when results are

Pharyngitis and Tonsillitis caused by S pyogenes.

Note: Penicillin is the usual drug of choice in the treatment of S pyogenes infections, including the prophylaxis of rheumatic fever. SUPRAX is generally effective in the eradication of S pyogenes from the nasopharynx; however, data establishing the efficacy of SUPRAX in the subsequent prevention of the property forms and published. of rheumatic fever are not available.

Uncomplicated Urinary Tract Infections caused by Escherichia coli and Proteus mirabilis
*Efficacy for this organism was studied in fewer than ten patients with otitis media.

CLINICAL STUDIES

In clinical trials of otitis media in nearly 400 children between the ages of 6 months and 10 years, Spneumoniae was isolated from 47% of the patients, H influenzae from 34%, B catarrhalis from 15%, and Spyogenes from 4%.

The overall response rate of *S pneumoniae* to cefixime was approximately 10% lower and that of Hinfluenzae or B catarrhalis approximately 7% higher (12% when beta-lactamase positive strains of Hinfluenzae are included) than the response rates of these organisms to the active control drugs. In these studies, patients were randomized and treated with either cefixime at dose regimens of

4 mg/kg bid or 8 mg/kg qd, or with a standard antibiotic regimen. Sixty-nine to 70% of the patients in each group had resolution of signs and symptoms of olitis media when evaluated two to four weeks posttreatment, but persistent effusion was found in 15% of the patients. When evaluated at the completion of therapy, 17% of patients receiving cefixime and 14% of patients receiving effective comparative drugs [18% including those patients who had *H influenzae* resistant to the control drug and who received the control antibiotic) were considered to be treatment failures. By the two- to four-week follow-up, a total of 30% to 31% of patients had evidence of either treatment failure or recurrent disease.

Bacteriological Outcome of Otitis Media at Two- to Four-Weeks Posttherapy Based on Repeat Middle Ear Fluid Culture or Extrapolation from Clinical Outcome

Organism	Cefixime ^(a) 4 mg/kg bid	Cefixime ^(a) 8 mg/kg qd	Control ^[a] drugs
Streptococcus pneumoniae Haemophilus influenzae	48/70 (69%)	18/22 (82%)	82/100 (82%)
beta-lactamase negative Haemophilus influenzae	24/34 (71%)	13/17 (76%)	23/34 (68%)
beta-lactamase positive Moraxella (Branhamella)	17/22 (77%)	9/12 (75%)	1/1(p)
catarrhalis	26/31 (84%)	5/5	18/24 (75%)
Streptococcus pyogenes	5/5	3/3	6/7
All Isolates	120/162 (74%)	48/59 (81%)	130/166 (78%)

Number eradicated/number isolated

An additional 20 beta-lactamase positive strains of *H influenzae* were isolated, but were excluded from this analysis because they were resistant to the control antibiotic. In 19 of these the clinical course could be assessed, and a favorable outcome occurred in 10. When these cases are included in the overall bacteriological evaluation of therapy with the control drugs.

140/185 (76%) of pathogens were considered to be eradicated.

Tablets should not be substituted for suspension when treating otitis media.

CONTRAINDICATIONS

llergy to cephalosporins.

WARNINGS

WARNINGS

BEFORE THERAPY WITH SUPRAX IS INSTITUTED, CAREFUL INQUIRY SHOULD BE
MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY
REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS
TO BE GIVEN TO PENICILLIN-SENSITIVE PATIENTS, CAUTION SHOULD BE EXERCISED
BECAUSE CROSS-HYPERSENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN
CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY
OF PENICILLIN ALLERGY. IF AN ALLERGIC REACTION TO SUPRAX OCCURS, DISCONTINUE THE DRUG. SERIOUS, ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE
TREATMENT WITH EPINEPHRINE AND OTHER EMERGENCY MEASURES, INCLUDING
OXYGEN, INTRAVENOUS FLUIDS, INTRAVENOUS ANTIHISTAMINES, CORTICOSTEROIDS,
PRESSOR AMINES, AND AIRWAY MANAGEMENT, AS CLINICALLY INDICATED.

Administer cautiously to allergic patients.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by Clostridium difficile is a primary cause of severe antibiotic-associated diarrhea including pseudomembranous colitis. Pseudomembranous colitis has been reported with the use of SUPRAX and other broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins). It is important to consider this diagnosis in patients who develop diarrhea in association with antibiotic use. Symptoms of pseudiagnosis in patients who develop diarrhea in association with antibiotic use. Symptoms of pseudomembranous colitis may occur during or after antibiotic treatment and may range in severity from mild to life threatening. Mild cases usually respond to drug discontinuation alone. Moderate-to-severe cases should be managed with fluid, electrolyte, and protein supplementation. When the colitis is not relieved by drug discontinuance, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile*. Other causes of colitis should be excluded.

General: Prolonged use may result in overgrowth of nonsusceptible organisms. If superinfection

General: Prolonged use may result in overgrown or nonsusceptible organisms, in superintection occurs, take appropriate measures.

Carefully monitor patients on dialysis. Adjust dosage of SUPRAX (cefixime) in patients with renal impairment and those undergoing continuous ambulatory peritoneal dialysis and hemodialysis.

[See DOSAGE AND ADMINISTRATION.]

[See DOSAGE AND ADMINISTRATION.]
Prescribe cautiously in patients with a history of gastrointestinal disease, particularly colitis.

Drug Interactions: No significant drug interactions have been reported to date.

Drug/Laboratory Test Interactions: A false-positive reaction for ketones in the urine may occur with tests using nitroprusside but not with those using nitroferricyanide.

SUPRAX administration may result in a false-positive reaction for glucose in the urine using Clinitest**, Benedict's solution, or Fehling's solution. Use glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix** or Tes-Tape***].

A false-positive direct Coombs test has been reported during treatment with other cephalosporin antibiotics; therefore, it should be recognized that a positive Coombs test may be due to the drug.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Although no lifetime animal studies have been conducted to evaluate carcinopanics opential in or mutagenic potential of SUPRAX was have been conducted to evaluate carcinogenic potential, no mutagenic potential of SUPRAX was found in standard laboratory tests. Reproductive studies revealed no fertility impairment in rats at

doses up to 125 times the adult therapeutic dose. **Usage in Pregnancy:** *Pregnancy Category B*: Reproduction studies have been performed in mice and rats at doses up to 400 times the human dose and have revealed no evidence of harm to the fetus due to SUPRAX.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: SUPRAX has not been studied for use during labor and delivery. Treatment should only be given if clearly needed.

Nursing Mothers: It is not known whether SUPRAX is excreted in human milk. Consider discontin-uing nursing temporarily during treatment with this drug.

Pediatric Use: Safety and effectiveness of SUPRAX in children aged less than 6 months have not

been established.

The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in pedi-ric patients receiving the suspension, was comparable to adult patients receiving tablets.

ADVERSE REACTIONS

Most adverse reactions observed in clinical trials were of a mild and transient nature. Less than four percent (4%) of patients in the US trials discontinued therapy because of drug-related adverse reactions. Commonly seen adverse reactions in US trials of the tablet formulation were gastrointestinal events, which were reported in 30% of adult patients on either the bid or the qd regimen. Clinically mild gastrointestinal side effects occurred in 20% of all patients, moderate events occurred in 9% of all patients, and severe adverse reactions occurred in 2% of all patients. Individual event rates included diarrhea 16%, loose or frequent stools 6%, abdominal pain 3%, nausea 7%, dyspepsia 3%, and flatulence 3%. The incidence of gastrointestinal adverse reactions, including diarrhea and loose stools, in pediatric patients receiving the suspension was comparable to adult patients receiving tablets

Symptoms usually responded to symptomatic therapy or ceased when SUPRAX was discontinued.

Several patients developed severe diarrhea and/or documented pseudomembranous colitis, and a few required hospitalization.

The following adverse reactions have been reported following the use of SUPRAX. Incidence rates were less than 1 in 50 (less than 2%), except as noted above for gastrointestinal events. Gastrointestinal: Diarrhea, loose stools, abdominal pain, dyspepsia, nausea, and vomiting. Several cases of documented pseudomembranous collits were identified during the studies. The onset of pseudomembranous colitis symptoms may occur during or after therapy. **Hypersensitivity Reactions:** Skin rashes, urticaria, drug fever, and pruritus.

Hepatic: Transient elevations in SGPT, SGOT, and alkaline phosphatase **Renal:** Transient elevations in BUN or creatinine.

Central Nervous System: Headaches 3%; dizziness

Hemic and Lymphatic Systems: Transient thrombocytopenia, leukopenia, and eosinophilia. Pro-

longation in prothrombin time was seen rarely. Other: Genital pruritus, vaginitis, candidiasis.

The following adverse reactions and altered laboratory tests have been reported for

cephalosporin-class antibiotics:

Adverse Reactions: Allergic reactions including anaphylaxis, Stevens-Johnson syndrome, ery

Adverse Reactions: Allergic reactions including anaphylaxis, Stevens-Johnson syndrome, erythema multiforme, toxic epidermal necrolysis, superinfection, renal dysfunction, toxic nephropathy,
hepatic dysfunction, including cholestasis, aplastic anemia, hemorlytic anemia, hemorhage.
Several cephalosporins have been implicated in triggering seizures, particularly in patients with
renal impairment when the dosage was not reduced [see DoSAGE AND ADMINISTRATION and
OVERDOSAGE]. If seizures associated with drug therapy occur, discontinue drug. Administer anticonvulsant therapy if clinically indicated.
Abnormal Laboratory Tests: Positive direct Coombs test, elevated bilirubin, elevated LDH, pancytesting in the properties of the particular direct combs.

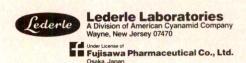
penia, agranulocytosis.

OVERDOSAGE

OVERDOSAGE
Gastric lavage may be indicated; otherwise, no specific antidote exists. Cefixime is not removed in significant quantities from the circulation by hemodialysis or peritoneal dialysis. Adverse reactions in small numbers of healthy adult volunteers receiving single doses up to 2 g of SUPRAX did not differ from the profile seen in patients treated at the recommended doses.

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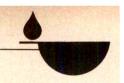
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TESTED BY SCIENCE AND TIME

Educational Interventions

Hugh D. Allen, MD, Columbus, Ohio Fredric Burg, MD, Philadelphia, Pa Harold Levine, MPA, Galveston, Tex Barbara Starfield, MD, Baltimore, Md Larrie W. Greenberg, MD, Washington, DC



Purpose.—This department is intended to share information concerning educational efforts in the broad field of pediatrics. We welcome studies on the following topics: undergraduate and graduate education in medicine and allied health occupations; continuing education of health professionals; education of patients and families; and health education for the general public, the community, and organizations that contribute to the promotion and improvement of the health of children.

Editorial Comment.—By nature, our young consider themselves invincible. AIDS doesn't care about invincibility. What is an adolescent population's knowledge about AIDS? Has it improved over time? If so, have attitudes changed? Steiner et al surveyed 1543 young people regarding these questions. See what happened.—H.D.A.

Are Adolescents Getting Smarter About Acquired Immunodeficiency Syndrome?

Changes in Knowledge and Attitude Over the Past 5 Years

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 A survey was administered to 1543 adolescents from southeastern Wisconsin to assess their knowledge, attitudes, and beliefs regarding acquired immmunodeficiency syndrome (AIDS) and persons with the disease. Responses were compared with those of other studies involving adolescents using identical or similar test items. Results of the study demonstrate that knowledge of AIDS and of the modes of human immunodeficiency virus transmission have increased dramatically over the past 5 years. Ninety-eight percent of high school students in this study understood the modes of transmission and that merely touching a person with AIDS will not transmit the virus. However, results also revealed that many negative biases remain toward people who have been infected with human immunodeficiency virus. Forty-five percent of the students believed that homosexuals and intravenous drug users were "getting what they deserve." Recommendations are made that future educational efforts focus on changes in attitudes and behaviors in relation to adolescents' previously acquired knowledge of AIDS.

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M any adolescents are at risk for exposure to the human immunodeficiency virus (HIV) because they experiment with high-risk behaviors such as intravenous (IV) drug use and unprotected sexual intercourse. Currently, approximately 21% of all acquired immunodeficiency syndrome (AIDS) cases are diagnosed in persons between 20 and 29 years of age,2 and many of these cases resulted from HIV infection during adolescence. These data have provoked a sense of urgency regarding adolescent AIDS education. Accordingly, educational programs have been instituted across the United States focusing on the modes of transmission of HIV and safer sex practices, since these are the mainstays of community prevention measures. 3-14

In spite of these intensive educational efforts, several investigators have demonstrated that even though education resulted in an increase in adolescents' knowledge about AIDS, many students continued to have misinformation and misunderstanding about AIDS. ¹⁵⁻¹⁸ A 1985 study of 250 high school students in Toledo, Ohio, found that many students lacked sufficient knowledge about AIDS, with a mean score of less than one half correct in a 19-item knowledge survey. Only 40% of the students surveyed knew AIDS could not be trans-

mitted via casual contact, and 31% thought AIDS could be cured. Less than one third of the students reported that schools were a primary source of their information. ¹⁵

In a similar study in 1986, 1326 San Francisco, Calif, high school students were shown to have marked inconsistencies in knowledge.16 Ninety-two percent of the students in the sample correctly responded that sexual intercourse was one mode of contracting AIDS, but only 60% knew the use of a condom during sexual intercourse may lower the risk of getting AIDS. Students were more informed about the modes of transmission of AIDS, but only 66% of the students surveyed knew AIDS was not spread through one's personal belongings, and only 68% knew that AIDS was not spread through casual contact. More recently, in a 1987 telephone survey of 829 teenagers in Massachusetts (70% of whom admitted to being sexually active), only 15% reported modifying their sexual practices and only 10% reported condom use.17 In a New York, NY, adolescent minority population, 73% of sexually active female adolescents did not insist that their partner use a condom the last time they had sexual relations. Seventy-one percent of the black female participants in the study reported that they were sexually active.19

It is apparent from these and other studies that more information is needed regarding the nature of adolescents' knowledge of and attitudes toward AIDS and persons with HIV infection. This information can be used to design additional educational programs tailored to correct specific areas of misinformation, increase basic knowledge, and change common adolescent patterns of risk behavior. This report describes the results of a large-scale survey of urban, suburban, and rural high school students. Data on participants' knowledge about AIDS and attitudes toward persons with the disease are presented and contrasted with other recent data. Implications for future AIDS education are discussed.

SUBJECTS AND METHODS Survey Instruments

The knowledge survey instrument was developed by the American Medical Students Association (AMSA)20 for use in the evaluation of adolescent AIDS education. This instrument consists of 15 true-false test items addressing popular misconceptions about the disease. The attitudinal survey was designed by a group of medical students at the Medical College of Wisconsin, Milwaukee, known as MCW CARES (Medical College of Wisconsin Council on AIDS Reaching Out and Educating Students) with advice and assistance from college faculty and staff. The survey was designed to assess the attitudes and perceptions of the participants toward AIDS and persons who have the disease. Like the AMSA Survey, the MCW CARES Attitude Toward AIDS Survey is a brief questionnaire, which can be administered quickly and is quite easy to complete.

A study of the validity of these two instruments was conducted before their use in the investigation. The validity investigation consisted of a careful content review for medical accuracy and correctness, and a review and analysis by test and survey experts to ensure psychometric quality. The review of the instruments revealed that it was necessary to compromise strict medical accuracy of terminology to provide items that could be readily understood by the adolescent participants. For example, the term AIDS is used throughout both surveys as an umbrella term for AIDS and HIV infection. While this terminology is not entirely accurate, initial discussions with students revealed that few of them were able to make the distinction between AIDS and HIV. In addition, both instruments were pilot tested and subject to revision prior to their use in the final data collection.

100	R	ural	Sub	Suburban		rban	
Age, y	Male	Female	Male	Female	Male	Female	Total
14	36	43	63	80	73	81	376
15	45	56	67	83	68	83	402
16	38	43	40	33	67	88	309
17	33	37	43	55	58	77	303
18	10	13	28	20	33	49	153
Total	162	192	241	271	299	378	1543

Table 2.—Results of the Survey of Adolescents' Knowledge and Attitude Acquired Immunodeficiency Syndrome (AIDS): Part I, Knowledge	
Knowledge Test	% Correct
AIDS is a life-threatening disease.	98
2. Everyone infected with the AIDS virus has become sick.	59
A person can get AIDS from donating blood.	63
4. If you touch someone with AIDS, you can get AIDS.	98
5. All homosexual men have AIDS.	94
6. Anybody can get AIDS.	94
7. AIDS can be spread by using someone's belongings, like a hairbrush.	97
8. Having sex with someone who has AIDS is one way of getting it.	98
AIDS can be cured if treated early.	93
10. If a pregnant woman has AIDS, there is a chance it may harm her unborn	
infant.	97
11. Using a condom during sex can lower the risk of getting AIDS.	96
12. You can get AIDS by sharing a drug needle.	97
13. People with AIDS may get other diseases because of AIDS.	79
14. A blood test can tell you if you will ever get AIDS.	83
15. People can be infected with AIDS without knowing it.	96

Study Participants

During 1988 to 1989, both surveys were administered as a pretest to students in 18 high schools throughout southeastern Wisconsin, including those in the Milwaukee-Chicago urban corridor and numerous surrounding suburbs and rural areas. The sample was not randomly selected, since schools were included on the basis of their participation in an AIDS education program. However, the schools included in the sample appear representative of other urban, suburban, and rural high schools in the United States. Participation and completion of the instrument was voluntary and anonymous, and 1543 of the 1715 high school students asked to participate were cooperative and willing to respond to the survey for a completion rate of 90%.

Table 1 provides a description of the high school students who completed the evaluation instrument. The group consisted of 1543 high school students ranging in age from 14 to 18 years. More female students (55%) than male students (45%) participated, and the largest number were from the urban areas (44%) as opposed to suburban (33%) or rural (23%) areas. Of the urban participants, 48% were black, 43% white, 7% Hispanic, and 2%

Asian/Oriental. The students from the suburban and rural areas were predominantly white.

RESULTS

The results of the analysis revealed that the majority of student respondents possessed extensive and accurate knowledge about AIDS. It was not surprising to find that older students (aged 17 and 18 years) knew more about AIDS than younger students (aged 15 and 16 years) and averaged two points higher on the knowledge scale (P<.05). No significant differences were detected, however, between the knowledge scores of male and female students or among students from rural, suburban, and urban schools.

A review of Table 2, which presents the AMSA Knowledge of AIDS Test, reveals that nearly all students participating in the study were aware of the seriousness of the disease, with 98% answering correctly that AIDS is a lifethreatening disease. The majority also knew that all homosexual men do not have AIDS. Most adolescents agreed

that "anybody can get AIDS" and, thus, that they could be at risk. The adolescent respondents also exhibited a considerable amount of knowledge of the disease, with 97% accurately answering that a pregnant woman can pass AIDS on to her unborn infant and 96% responding that a person can be infected with AIDS without knowing it.

The respondents were also well informed regarding the modes of transmission of HIV. For example, questions 4 and 7 of Table 2 pertain to the transmission of AIDS through casual contact. Ninety-eight percent of the respondents answered correctly that merely touching a person with AIDS or his or her belongings will not transmit the disease. In addition, the student respondents seemed to understand about the nature of high-risk behaviors. Ninety-eight percent agreed that AIDS can be transmitted by sexual intercourse and sharing an IV drug needle. Ninetysix percent agreed that using a condom during sexual intercourse can lower the risk of transmission.

While respondents were well informed about some aspects of the disease, such as modes of transmission, they were less informed about the clinical course of HIV infection. For example, only 60% of the respondents knew that not everyone infected with AIDS has become sick. Respondents were also confused about the process of donating blood and receiving blood transfusions. Thirty-seven percent believed that a person can get AIDS from donating blood. In addition, some students were confused about the nature of testing, with only 83% correctly answering that a blood test cannot predict whether a person will ever get AIDS.

The results of the Attitude Questionnaire of the MCW CARES Attitude Toward AIDS Survey are presented in Table 3. Most students appear to have a positive attitude toward the disease and persons who have AIDS. The majority believe that children with AIDS should be allowed to attend school (80%) and do not believe that persons with AIDS should be quarantined or isolated (83%). The majority (84%) also disagree with the statement "too much time and money is being devoted to the disease." Responses to the attitude scale items, however, reveal that some fear persists.

Table 3.—Results of the Survey of Adolescents' Knowledge and Attitude Toward Acquired Immunodeficiency Syndrome (AIDS): Part II, Attitudes

Attitude Item	% Agreement
1. Homosexuals and intravenous drug users who contract AIDS are gettin	g what
they deserve.	45
AIDS is God's way of punishing people for their evil acts.	14
3. My feelings toward people with AIDS depends on how they got the dise	ease. 56
 Students who have AIDS should be allowed to attend school. 	80
5. Too much time, money, and other resources are being devoted to A	IDS in
comparison with other diseases.	16
I would refuse to sit next to a person who has AIDS.	18
People who have AIDS should be isolated for the safety of others.	17
8. AIDS is a disease commonly found in New York and California and	is not
something people in my community need worry about.	9
9. I would feel uncomfortable using the same lavoratory and locker ro	om as
people with AIDS.	55
10. I would feel more sympathy toward a person who got AIDS from	blood
transfusion than from drug abuse or sexual activity.	76

For example, the respondents seem to feel comfortable sitting next to a person with AIDS (only 18% would refuse), but only half would feel comfortable using the same locker room or lavatory facilities. The respondents also exhibit some negative attitudes and persistent biases. While the majority do not agree with the statement "AIDS is God's way of punishing people for their evil acts," almost half (45%) believe that homosexuals and IV drug users are getting what they deserve. Also, most (76%) of the students who responded expressed that they would feel more sympathy for persons who contracted AIDS from a transfusion than from drug use or sexual activity.

Follow-up analysis failed to reveal significant differences in the attitudes of students of the various age groups or among students from rural, suburban, and urban schools. However, the analysis did reveal a notable difference in the attitudes of the male and female participants. The overall mean score of the male participants on the four-point attitude scale (4 indicating positive; 1, negative) was found to be 2.54 compared with the female participants' score of 3.12. These differences were found to be statistically significant (P<.05).

COMMENT

The results of this survey have important implications for present and future adolescent AIDS education. The high school students appear to possess a good fund of knowledge of the nature of the disease and of how it is transmitted. They know that AIDS is not passed from one person to another through ca-

sual contact, and that certain high-risk behaviors, such as IV drug use and unprotected sexual intercourse, are associated with the spread of the disease. No differences were found in the knowledge level of students from rural, suburban, and urban schools or between male and female students. As expected, older students scored somewhat higher than younger students.

In spite of the extensive knowledge that these students seem to possess, they are confused about several other areas and also hold some negative attitudes and popular biases against AIDS and persons with AIDS. These results can be juxtaposed to those found by other researchers.

Table 4 provides a comparison of the results of this study with four previous studies of the knowledge and attitudes of adolescents toward AIDS. While these studies cannot be directly compared with the present study, since they were conducted with different populations in different locations, they are offered here to add a historic dimension. The findings of the studies can be divided into three critical areas: modes of transmission, knowledge, and attitudes. In the earlier studies, adolescent respondents answered fewer items correctly than in more recent studies. For example, only 40% of the respondents in the study conducted by Price et al¹⁵ in 1985 were aware that AIDS is not transmitted by casual contact. Two years later, 75% of the respondents in another study answered this statement correctly. This response rate increased to 92% correct in the 1988 Centers for Disease Control, Atlanta, Ga, study,18 and to

Table 4. - Summary of Adolescents' Knowledge and Attitudes About Acquired Immunodeficiency Syndrome (AIDS)

			Source, y		
Variable	Price et al,15 1985 (n = 250)	DiClemente et al, ¹⁶ 1986 (n = 1326)	Strunin and Hingson, ¹⁷ 1987 (n = 963)	Centers for Disease Control, ¹⁰ 1988 (n = 35 239)	Current Study, (n = 1543)
CONTRACTOR OF THE PARTY OF THE		Modes of Transmissio	n, % Correct		
Sexual contact		92	92	94	98
2. Intravenous drug use		81	91	94	97
3. Casual contact	40	75	93	92	98
4. Pregnant woman can					
give AIDS to infant		86			97
5. Condom use lowers					
transmission		60			96
transmission				S C TO SHOULD BE	RESIDENCE OF SHIP
	70	General Knowledge, 84			98
1. AIDS is fatal	76	84			
2. AIDS is not inherited	81	61			93
3. No cure for AIDS	69	ы			30
4. AIDS causes other		07			79
diseases		37	A LONG MARKET		94
Anybody can get AIDS	***	85		and the second second second	94
6. Can get AIDS by			00	10	63
donating blood	Combined to the second		38	40	03
		Attitudes, % Co	orrect		
All homosexual men					0.1
have AIDS		80			94
2. Allow a child with AIDS					
to attend school	A 144	77		White the same of the same	80
3. Important to receive					
AIDS education		87	97		84
4. Worried about getting					
AIDS	27	66	54		91

98% correct in the current study. Also, the concept that sexual contact and IV drug use are high-risk behaviors for AIDS increased from 92% and 81% correct to 98% and 97% correct, respectively. Knowledge of the fact that AIDS is fatal and incurable shows corresponding trends. It is interesting to note that many (37%) adolescents continue to think that one can acquire HIV from blood donation. This may have important implications for the availability of blood products, since high school blood drives have traditionally been an important source of donated blood. For example, the Blood Center of Southeastern Wisconsin reports that nearly 10% of all donated blood comes from local high school blood drives.

Considering the emphasis given to AIDS education in the community and the schools, it is gratifying to discover that high school students in 1989 know more about AIDS and how it is transmitted than high school students did in 1985. Unfortunately, these theoretical gains in knowledge do not appear to carry over into attitudes about AIDS or persons with the disease. A review of Table 4 indicates that, in general, atti-

tudes have not changed across these studies; perceptions of persons with AIDS are still somewhat negative and coincide with popular biases. For example, the 1986 study of DiClemente et al16 found that only 77% of the respondents would allow a child with AIDS to attend school. The results of the current study indicate that approximately 20% would still bar the school doors against HIVinfected children. The students' attitudes in this regard appear contradictory, since 98% are aware that AIDS is not transmitted through casual contact. Another gap between knowledge and attitudes is the students' reluctance to share, evidenced through their lack of willingness to share lavatory or locker room facilities with persons having AIDS. However, students' responses to the question regarding concern about contracting AIDS shows a fairly dramatic increase in positive attitudes. Twenty-seven percent of the participants in the 1985 study of Price et al15 expressed concern about getting AIDS. This proportion increased to 66% in the 1986 study of DiClemente et al, and was 91% in the MCW sample. Responses to this item should be interpreted cautiously, however, since students' responses may be influenced by their perception of the socially responsible answer. For example, some students may associate fear of getting AIDS with indulgence in behaviors that they view as not socially acceptable. A male adolescent admitting that he is afraid of getting AIDS may have fear of being accused of homosexuality or IV drug use. Students' responses regarding their fear of getting AIDS should also be interpreted in light of the fact that the male student participants evidenced a significantly more negative attitude than the female participants toward the disease and persons who have it. Other researchers have found that men tend to be more homophobic than women,6 and students' responses may be affected by perceptions that AIDS is closely associated with homosexuality. This interpretation corresponds to the large number of MCW study respondents who apparently condemn homosexuals and IV drug users who contract AIDS and agree (45%) with the statement that they are getting what they deserve, and the 56% who express the belief that the sympathy they would feel toward a person with AIDS depends on how the person got the disease. This interpretation is bolstered by the fact that 76% of the respondents stated they would feel more sympathy toward a person who got AIDS from a blood transfusion than from drug abuse or sexual activity.

These findings should be interpreted with caution, since the study has certain limitations. The sample employed was drawn exclusively from southeastern Wisconsin and may not be generalizable to the national population of adolescents. It must also be recognized that a large proportion of adolescents who are most "at risk" for contracting HIV may not be readily assessed through the schools. The study is further limited by the lack of precision of the knowledge and attitude surveys employed. This was unavoidable since it was necessary that they be designed for ease of understanding and completion. In addition, the use of the term AIDS as a catchall term for any HIV infection may be problematic and lead to confusion in comparing studies across populations.

CONCLUSIONS

The results of the current study and the work of other researchers reveal that media coverage and educational efforts to communicate AIDS information to adolescents have achieved a measure of success. There seems to be an in-

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crease in knowledge over time, and many adolescents apparently are quite well informed about the nature of the disease and how it is transmitted. However, the results of this study and others also reveal that adolescents, especially male, still possess substantial negative attitudes and biases regarding people with AIDS. These negative attitudes appear to be linked with negative attitudes toward homosexuals and IV drug users. These results suggest that future AIDS education programs should emphasize compassionate and positive attitudes toward persons who have the disease regardless of how they contracted it. Educational interventions should recognize the fact that adolescent males may be homophobic. While it is important that future programs reinforce adolescents' knowledge about the disease, it has been demonstrated that knowledge possessed by adolescents may not necessarily modify their behavior or attitudes. 14,21 It may well be that an "incubation" period is needed for this knowledge to affect behavior. The model for smoking prevention suggests that it takes several years for the population to curtail high-risk behavior once it has become informed of the hazards involved.22

Current AIDS education programs have stressed very elementary concepts about the nature of HIV infection

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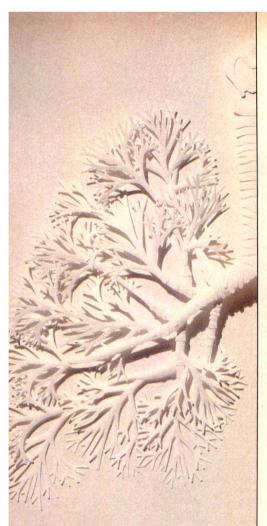
and modes of transmission. As evidenced by the results of the survey described in this article, adolescents appear to have mastered this information. It may be, however, that more specific and in-depth information is needed to affect a change in attitudes or behaviors of these students. Future efforts also should be directed toward identifying high-risk adolescents who may not be currently accessible through conventional educational programs such as high school health or physical education classes. Some type of intervention program may be needed to reach this group and convince them of the perils of highrisk behaviors.

This study shows that educational efforts have clearly succeeded in teaching adolescents some important facts about HIV infection. The ultimate goal of adolescent AIDS education, however, is to reduce the incidence of the disease in the population. Educational efforts have not yet been proved sufficient to change attitudes and high-risk behaviors. It is therefore imperative that future interventions be directed toward achieving changes in attitudes and behaviors in relation to adolescents' previously acquired knowledge about AIDS.

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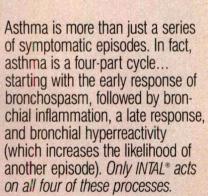
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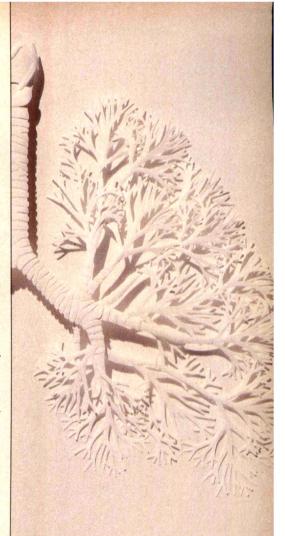


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CONTRAINDICATIONS: INTAL Inhaler is contraindicated in those patients who have shown hypersensitivity to cromolyn sodium or other components

WARNINGS: INTAL Inhaler has no role in the treatment of an acute attack of asthma, especially status asthmaticus. Severe anaphylactic reactions can occur after cromolyn sodium administration. The recommended dosage should be decreased in patients with decreased renal or hepatic function. INTAL Inhaler should be discontinued if the patient develops esoinophilic pneumonia (or pulmonary infiltrates with esoinophilia). Because of the propellants in this preparation, it should be used with caution in patients with coronary artery disease or a history of cardiac arrhythmias.

PRECAUTIONS: General: In view of the biliary and renal routes of excretion for cromolyn sodium, consideration should be given to decreasing the dosage or discontinuing the administration of the drug in patients with impaired renal or hepatic function.

Occasionally, patients may experience cough and/or bronchospasm following cromolyn sodium inhalation. At times, patients who develop bronchospasm may not be able to continue administration despite prior bronchodilator administration. Rarely, very severe bronchospasm has been encountered.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long term studies in mice (12 months intraperitoneal treatment followed by 6 months observation), hamsters (12 months intraperitoneal treatment followed by 12 months observation), and rats (18 months subcutaneous treatment) showed no neoplastic effect of cromolyn sodium. No evidence of chromosomal damage or cytotoxicity was obtained in various mutagenesis studies. No evidence of impaired fertility was shown in laboratory animal reproduction studies.

Pregnancy: Pregnancy Category B. Reproduction studies with cromolyn sodium administered parenterally to preg-Pregnancy: Pregnancy Category 6 American Consider the American Consideration and miscrete parenterally to pregnant mice, rats, and rabbits in doses up to 338 times the human clinical doses produced no evidence of fetal malformations. Adverse fetal effects (increased resorptions and decreased fetal weight) were noted only at the very high parenteral doses that produced maternal toxicity. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Drug Interaction During Pregnancy: Cromolyn sodium and isoproterenol were studied following subcutaneous injections in pregnant mice. Cromolyn sodium alone in doses of 60 to 540 mg/kg (38 to 338 times the human dose) did not cause significant increases in resorptions or major malformations. Isoproterenol alone at a dose of 2.7 mg/kg (90 times the human dose) increased both resorptions and malformations. The addition of cromolyn sodium (338 times the human dose) to isoproterenol (90 times the human dose) appears to have increased the incidence of both resorptions and malformations.

Nursing Mothers: It is not known whether this drug is excreted in human milk, therefore, caution should be exe when INTAL Inhaler is administered to a nursing woman and the attending physician must make a benefit/risk assessment in regard to its use in this situation.

Pediatric Use: Safety and effectiveness in children below the age of 5 years have not been established. For young children unable to utilize the Inhaler, INTAL Nebulizer Solution (cromolyn sodium inhalation, USP) is recommended. Because of the possibility that adverse effects of this drug could become apparent only after many years, a benefit/risk consideration of the long-term use of INTAL Inhaler is particularly important in pediatric patients.

ADVERSE REACTIONS: In controlled clinical studies of INTAL Inhaler, the most frequently reported adverse reac-tions attributed to cromolyn sodium treatment were: throat irritation or dryness, bad taste, cough, wheeze, nausea. The most frequently reported adverse reactions attributed to other forms of cromolyn sodium (on the basis of

The most regiquenty reported adverse reactions artifulated to their forms of clondry) soudinf or me basis of reoccurrence following readministration) involve the respiratory tract and are: bronchospasm [sometimes severe, associated with a precipitous fall in pulmonary function (FEV.)], cough, laryngeal edema (rare), nasal congestion (sometimes severe), pharyngeal irritation and wheezing.

Adverse reactions which occur infrequently and are associated with administration of the drug are: anaphylaxis, angioedema, dizziness, dysuria and urinary frequency, joint swelling and pain, lacrimation, nausea and headache, rash, swollen parotid gland, uricaria, pulmonary infilitrates with esoinophilia, substernal burning, and myopatche. The following adverse reactions have been reported as rare events and it is unclear whether they are attributable to the drug acceptance melalicial complexities. In a proposition of the drug acceptance in a proposition of the drug acceptance in a proposition and proposition of the drug acceptance in a proposition and proposition are proposition and proposition and proposition are propositional proposition and prop

the drug; anemia, extoliative dermatitis, hemoptysis, hoarseness, myalgia, nephrosis, periarteritic vasculitis, pericarditis, peripheral neuritis, photodermatitis, sneezing, drowsiness, nasal itching, nasal bleeding, nasal burning, serum sickness, stomach ache, polymyositis, vertigo, and liver disease.

OVERDOSAGE: No action other than medical observation should be necessary.

DOSAGE AND ADMINISTRATION: For management of bronchial asthma in adults and children (5 years of age and

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Reference: 1. Eigen H, Reid JJ, Dahl R, et al: Evaluation of the addition of cromolyn sodium to bronchedilator maintenance therapy in the long-term management of asthma. J Allergy Clin Immunol 1987:80:612-621

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Suicide Attempts Among Adolescent Drug Users

Alan L. Berman, PhD, Richard H. Schwartz, MD

 Substance use has been identified as a significant risk factor in nonfatal and fatal suicides during adolescence. A comprehensive questionnaire on patterns of alcohol and other drug use, early childhood and nuclear family psychological and behavioral history, and previous suicidal attempts was completed by 298 (88%) of 340 outpatient adolescent substance abusers in three geographic regions east of the Mississippi River. An abbreviated Beck Depression Inventory was included to ascertain current symptoms of depressed mood. Adolescents admitting to a previous suicide attempt (30%) were compared with two age- and sex-matched samples. Substance abusers were three times as likely as a normative population of non-drug-using ageand sex-matched peers to make a suicide attempt. Thirty-three percent of attempts reported occurred prior to high school. Both the wish to hurt oneself and actual suicide attempts were found to increase significantly after the initiation of substance use. Forty percent used drugs within 8 hours before the suicide attempt, and 23% of attempters reported that their families continued to have a firearm with ammunition in the home following the suicide attempt. Adolescent substance abusers who had attempted suicide were significantly more likely than a matched group of nonattempters in the same drug treatment facility to: (1) complain of usually feeling "blue" or sad (depressed affect) during early childhood, (2) identify important childhood behavioral problems, (3) identify long-standing self-perceived impaired self-concept, and (4) identify serious parental problems, such as chronic depression or alcoholism. Self-perceived chronic loneliness in childhood appears to be a singularly important initiator of adolescent drug use and subsequent suicide attempts among drug abusers.

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The widespread use of alcohol and other intoxicating drugs by teenagers has been cited as one of the most influential factors contributing to increased rates of adolescent suicide. ¹⁻⁵ Nationwide, suicide is currently the third leading cause of death for the 15- to 24-year-old age group, and in Virginia suicide is the second leading cause of death in this age group. Among adolescents who attempt suicide, those who use illicit drugs outnumber controls by 8 to 1 to 10 to 1.⁶ The relationship between substance abuse and risk of suicide, however, is complex.

It is generally agreed that there is a progressive increase in depressed mood from abstainer to substance user and a corresponding increase in suicide attempts among adolescents with depression, substance abuse, or both. Little is known about possible differences in early childhood and adolescent experiences between adolescent drug abusers who attempt suicide and adolescents who abuse drugs but do not attempt suicide or adolescents who do not abuse drugs. This study examines these relationships in a large sample of middle-class adolescent drug abusers and through three case-control comparisons.

STUDY DESIGN AND PATIENT POPULATION

An extensive written questionnaire on patterns of substance use, family and behavioral history, and suicidal behavior and history was administered to 340 adolescent drug users over a 4-month period between December 1987 and March 1988. Included in the survey instrument was the short form (16-item) Beck Depression Inventory, a validated self-administered list of multiple choice questions on current mood state, sleep and appetite, and optimism vs hopelessness, etc. ⁷

The respondents were enrolled in four long-term, modified outpatient, family-oriented drug-abuse treatment facilities located in three regions of the country (Mid-Atlantic, South, and Great Lakes). On admission to the drug-abuse treatment facility, every adolescent was interviewed in depth by a psy-

chiatrist, and the diagnosis was coded according the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R), published by the American Psychiatric Association, Washington, DC. After written consent agreements had been obtained both from respondents and their parents, the survey instrument was distributed to respondents while they were attending large group therapy sessions in their facilities. The study had the approval of the Institutional Review Board of Straight Inc, located in Springfield, Va. An additional sample of 105 consecutive adolescent outpatients was secured from a suburban pediatric practice to serve as one of the control groups. Verbal permission was obtained from parents and adolescents in the private practice setting to allow the adolescents to complete, in private, a list of 32 questions on the presence of important early childhood and family problems. The questions were identical to the early childhood and family questions answered by the participants in the drug-abusing study groups.

The data were entered into a computer system and analyzed using the Statistical Package for the Social Sciences. Incomplete questionnaires and those with important inconsistent answers to internal validatory questions were deleted from these analyses. Results are reported for: (1) the drug-using population as a whole, (2) the sample of drug users who reported making one or more suicide attempts, and (3) three case-control comparisons: (a) drug-using adolescents who had attempted suicide vs a matched sample of non-drug-using adolescent outpatients, (b) drug-using youths who had attempted suicide vs a matched sample of drug-using nonattempters, and (c) drug-using suicide attempters-those who had made single attempts vs multiple attempters.

RESULTS

Two hundred ninety-eight (88%) drug-abusing adolescent patients completed usable questionnaires. The subjects ranged in age from 13 to 19 years, with a median of 16.2 years. The sample was overwhelmingly white (93%) and predominantly male (66%).

The drugs of choice were marijuana and/or hashish (61%) and alcohol (31%).

Sixty percent of the subjects used intoxicants at least once per day.

Two thirds (67%) of the sample reported previous suicide *ideation*, the majority during the years of drug use. Thirty percent of the 298 drug users (n=89) reported at least one previous suicide *attempt*, excluding skin carving; 25 (28%) of these youths had made multiple attempts.

Suicide Attempt Subsample

The 89 self-reported suicide attempters were significantly more likely than nonattempters to be female (56% female [50 respondents] vs 44% male [39 respondents]; $\chi^2 = 39.97$, df = 3, P < .001). About one fourth of these attempters recalled that both the wish to hurt themselves and a suicide attempt occurred prior to their involvement with drugs; however, these proportions increased to 70% (wish, 62 respondents) and 90% (attempt, 80 respondents) during their years of drug use. Thirty-three percent of the reported first suicide attempts (29 attempts) occurred prior to high school entry. The majority of attempters performed poorly (minimum of 2D grades) in school during the term preceding their first attempt. The majority (63 attempters [71%]) had contact with the mental health treatment system prior to their first attempt. Satanic music is believed to be associated with adolescent suicide because of the nihilistic lyrics repetitively suggesting that suicide is a viable option to put an end to unbearable emotional pain during adolescence. Twenty-five percent of the respondents (22 respondents) stated that they were "really into satanic music" before they attempted suicide. Selfharm behaviors were commonplace, and 29% of the respondents (26 respondents) had "carved" in their flesh before their first or only suicide attempt. In the 2 weeks prior to their first attempt, these youths reported that they "felt no one understood [them]" (74 respondents [83%]), "were depressed most of the time" (73 respondents [82%]), "felt hopeless" (63 respondents [71%]), and had significant symptoms of depression: poor concentration in school (54 respondents [61%]), lack of energy (50 respondents [56%]), and trouble sleeping (34 respondents [38%]).

Forty percent (33 respondents) used

drugs within 8 hours before their attempt: the attempts occurred mostly at home (68 respondents [78%]). Most attempters (72 respondents [81%]) lived with one or more parents. Forty-two percent (37 respondents) were alone at the time of their suicide attempt. Among the most frequent precipitating events and experiences were feelings of hopelessness and loss of interest in usual activities (64 respondents [72%]), isolation from parents (51 respondents [57%]) and friends (27 respondents [30%]), serious school problems (51 respondents [57%]), serious fights with a parent (50 respondents [56%]), and "breaking up" of a romantic relationship shortly preceding the suicide attempt (28 respondents [31%]), Only 17% (15 respondents) of those who admitted to a previous suicide attempt left a farewell note, and only 7% (6 respondents) gave away or sold their special belongings immediately prior to the suicide attempt. Forty-two percent (37 respondents) reported being preoccupied with thoughts of death for several weeks or months prior to their attempt but most had no specific plans. Nearly half (43 respondents [48%]) of the sample reported knowing someone who had completed suicide before the date of their first attempt, and 19% (17 respondents) of these subjects' attempts occurred within 1 year of that exposure.

Seventy-eight percent of attempts (69 attempts) occurred after drug use began. The majority of these attempts were of low lethality (the modal method was drug ingestion), with 61% (54 attempts) requiring no medical attention. However, 10% (9 respondents) tried to kill themselves by a motor vehicle, 8% (7 respondents) attempted to hang themselves, and 15% (13 respondents) claimed that they were unconscious after the suicide attempt. Forty-three percent (38 respondents) told someone right away, another 24% (20 respondents) were "discovered," and for 19% (17 respondents) the attempt remained a secret. Only one of the adolescents in our survey called a suicide "hotline" telephone number. Parents of 35% (31 respondents) of these attempters "never found out."

About half (41 attempters [46%]) of the attempters viewed the purpose of their attempt as a "cry for help," with 81% (72 respondents) reporting that they really did not want to die. Fortytwo percent (37 respondents) intended their attempt "to stop the (emotional) pain." Forty-five percent (40 respondents) believed their attempt was related to a long-term depression that had begun before drug use. Of special interest with respect to the possibility of subsequent attempts is that 23% (20 respondents) reported that their families kept a firearm with ammunition, and 46% (41 respondents) reported that lethal means other than firearms were available to them in their home after their suicide attempt.

Case-Control Comparisons

Attempters vs Nonattempters.—A subsample of 54 drug-using suicide attempters was matched by age, gender, and race with 54 drug-abusing nonattempters who were in the same drugabuse treatment facility. Results from the modified Beck Depression Inventory found a significant difference (F=3.96, P<.05) between these groups, with attempters scoring at a higher (more depressed) level than nonattempters. In addition, χ^2 tests documented significant differences (P<.05) between attempters and nonattempters in ascribing the following problems to their preteen years: belief that one was "really ugly," a serious learning disability, loneliness, puzzling mood swings by age 10 to 11 years, serious parental conflicts, temper tantrums, being accident prone, and a chronic disease (eg, asthma. Nonattempters were significantly more likely than attempters to agree with the statement "I was an average child without any really important problems."

Moreover, χ^2 comparisons showed that drug-using attempters were significantly more likely than nonattempters to describe wishes to hurt themselves both before (30% vs 6%, $P \le .001$) and during (89% vs 36%, P < .001) the years of their drug use. These differences remained even after an average of 5 months of treatment (41% vs 19%, $P \le .02$). Consistent with their elevated Beck scores, the attempters continued to have significantly more suicide ideation during their drug treatment.

Drug-Using Attempters vs Non-Drug-Using Controls.—Matched (by

age, gender, and race) samples of drugabusing attempters (in treatment) and non-drug-using "normative" controls (n=69) were compared on a 32-item list of childhood problems, experiences, behaviors, and feelings. Attempters differed significantly from controls (P<.05) on 24 of these comparisons, including those reflecting problems of conduct, behavioral control, and anger management (frequent dishonesty, frequent temper tantrums, violent temper, disobedience at school, frequent stealing, trouble with the law, being accident prone, hyperactivity); affect (puzzling mood swings, depression and persistent sadness); isolation (loneliness, noninvolvement in sports or hobbies); feelings and beliefs about self (problems learning from mistakes; belief that "I was really ugly," that "people did not like me," that "I had a serious learning disability," that "I was difficult to raise," that "I was not an average child"); and problems with and within the parental system (felt rejected, parents had serious conflicts, parent had alcohol and/or drug problem, father hated his job). Twenty-three percent (16 respondents) of the drug users reported a history of sexual abuse (by anyone, but most often by a relative or by a baby-sitter) vs 1% (1 respondent) of controls. The item most frequently noted by the drug-using attempters was experiencing loneliness in their childhood (55 respondents [79%] vs 13 controls [19%]). This item and that of "puzzling mood swings" were the items most frequently ascribed to by drug-using attempters as well as being statistically significant in case-control comparisons.

Single vs Multiple Attempters.—A subsample of 18 (of 25) multiple (repeated) attempters was matched (by age, gender, and race) with 18 single attempters. Statistical comparisons were limited by the small sample size. No difference was found between groups on the Beck Depression Inventory (F = 0.72, not significant), nor were there differences in the proportions of those reporting a wish to hurt themselves before or during drug usage and during treatment. In contrast to multiple attempters, single attempters were more likely to come from families where a parent used drugs (8 respondents [44%] vs 2 respondents [11%], P = .03 by

one-tailed Fisher's Exact Test) and to report that weapons or other means of suicide had been removed from their homes after their first attempt (14 respondents [78%] vs 6 respondents [33%], P < .02). Multiple attempters were more likely than single attempters to have had trouble concentrating in school within 2 weeks of their first attempt (P < .02) and to have seen a psychiatrist after their first attempt (P < .04). The following trends were noted but did not achieve statistical significance: multiple attempters believed their first attempt was related to problems in childhood, were depressed before initiating drug usage, were accident prone before drug usage, and had been physically injured before their first attempt.

COMMENT

Illicit drug use has become widespread among adolescents in the last two decades. 8-12 More recent surveys document a decline nationwide from peak usage in the late 1970s (Washington Post. March 7, 1989; "Health" section, p 8).13 Among the many predictors of drug initiation during adolescence are parental alcoholism and/or drug abuse: childhood delinquency; recurrent impulsive and dangerous thrilling risktaking behaviors during childhood and early adolescence; the extent of malevolent influence of the young adolescent's peer group; deviant personality or character traits, including low self-esteem; and childhood and adolescent depression. Additional parental factors (eg, discordant marital relationships or a serious mismatch of parent/child temperament, also appear to be important risk factors for an adolescent to seek solace from drugs and drug-abusing peers. 14,15 Inherent in these predictors are some of the possible links between substance use/abuse and suicide. For example, they may share an underlying pathologic condition such as depression, both may serve as maladaptive coping mechanisms mediated and precipitated by environmental stress, both may be variants and outcomes of antisocial behavior, and/or both may have as precursors genetics or parental modeling.16

Although the specific mechanism of influence is unclear, the parental system, particularly parental substance

abuse, including alcoholism, is an important factor in the etiology of adolescent substance abuse and in adolescent suicidal behavior. The relationship is well substantiated by reports of high rates of substance abuse among parents of adolescents who abuse drugs. 12,17 Additionally, there is substantial evidence that parents of children and adolescents who attempt suicide abuse drugs more frequently than parents of nonattempting youth, 18-20 with rates of abuse among the former ranging from 31% to 44%. 18,21,22

The possible mediating role of depression between substance use and suicidal behavior is of particular interest. Numerous studies of adults in treatment for drug abuse have documented at least moderate depression in 30% to 55% of these patients. 22-24 Among adolescents, depression is reported to be greater among drug abusers than nonusers25 and among those who are abusive drinkers of alcohol-containing beverages vs those who are restrained drinkers.12 Although substance use appears to be clinically associated with depression, it remains unclear whether depression is primary^{3,25-81} (ie, whether drug use represents, for some as yet unknown percentage of adolescent drug abusers, an effort at self-medication to regulate chronic depressed affect) or whether substance abuse is primary (eg, depression is one important effect of binge or chronic use of alcohol, marijuana, LSD, phencyclidine (PCP), or stimulant drugs such as cocaine). 32-34 Admission to a drug-treatment facility, particularly one that separates adolescents from their friends, family, and social milieu, is in itself a major cause of and confounding variable for depressive affect. Drug use may be mediated by interpersonal loss; as a depressive spectrum disease, 35 alcoholism has been found to lead to major life-style changes (eg. disrupted interpersonal relationships), which, in turn, lead to depression, despair, and, consequently, increased suicidality. 36,37

Drug-related emergency department visits and inpatient admissions have increased, as has drug-related mortality. 10,88 Drug ingestion is the overwhelming method of choice among adolescents who attempt suicide; it currently accounts for 71% to 88% of such adolescents who present for emergency department treatment. 39-41 As the age of initiation of substance use decreases, the prevalence of later social consequences increases. 42 As "gateway substances," marijuana and alcohol represent significant foci for both public and mental health prevention efforts.

Motivations for early use of drugs are primarily psychological (eg, the desire to fit in or feel older, the desire to rebel against parental and school authority, and, especially, succumbing to peer pressure, ie, initiating use and continuing to use drugs because valued friends are using drugs and extolling the "pleasures" of being intoxicated. Motivations may also include the self-perceived need or drive to self-medicate a latent or overt depression. Psychological distress is likewise a significant precursor to drug involvement. Among the untoward effects of substance use in adolescence is a manifest depression and the possibility of consequent suicidality. Adverse health behaviors in adolescence are highly intercorrelated and often are accompanied by feelings of hopelessness and suicidal ideation.48 It is not surprising, then, that substance use, depression, and antisocial behavior present concurrently and that, independently and in combination, they are significant co-occurring pathologic conditions with suicide attempts and completions in adolescence. One study³⁸ reporting a 6-year comparison (1980-1982 vs 1974-1976) of 900 adolescent inpatients found concurrent increases in admission diagnoses of depression (a 350% increase), substance abuse (a 200% increase), and suicide ideation (a 200% increase). Embedded as intervening variables among and common to these psychopathologic conditions and symptom presentations are cognitive distortions, impulsivity, frequent and serious interpersonal loss, family social dysfunction (including possible biological and modeling influences), and male gender.

Results of our surveys of adolescent drug users have shown that two thirds of these users report suicide ideation and 30% report having made one or more suicide attempts, mostly of low lethality. This frequency of suicide ideation is greater than that reported among most samples of normal adoles-

cents, with studies finding a prevalence of ideation ranging between 23% and 52%, 43-45 The proportion (30%) reporting an attempt is three times greater than frequencies of attempt found in samples of normal adolescents, who have a reported prevalence of 7% to 9%.447 Although signs and symptoms of depression were reported as quite prevalent in childhood and prior to the onset of drug use, suicide ideation and behavior increased significantly during the years of drug use. If substance use is intended as a self-medication of an underlying depression, it evidently fails miserably in accomplishing this purpose; instead, it appears to potentiate suicidality.

Among documented risk factors, drug-using suicide attempters, as documented by our study, are more likely than nonattempters to be female, to report more signs and symptoms of depression and behavioral disturbance in childhood, and to perceive greater and more frequent problems in self-concept and in their parental systems.

Significant among these problems and of possible special interest is the great number of attempters who report loneliness as a problem of childhood. Although there is substantial overlap between loneliness and depression, 48 they generally are considered to be separate constructs. Loneliness involves the absence or perceived absence of satisfying social relationships, accompanied by negative affect (anxiety, distress, depression).48 Those who are not distressed by conditions of social deprivation are not lonely. This negative affect may be a way to cope with the experience of loneliness, which, in turn, may involve interpretations (attributions) to explain aloneness or unsatisfying social relationships. Of particular interest to us is that the significant aspect of loneliness is the absence of social reinforcement or the presence of nonreinforcing social experiences. These may be the primary motivators for the adolescent to associate with drug-using peers who may initiate and/or reinforce drug use. Kaplan et al49 recently posed and tested just this sort of path model to explain adolescent drug use. In this model, early perceived experiences of rejection, failure, and punishment in conventional social groups (school and family) lead to increasing alienation from these groups and a concurrent disposition to engage in deviant behavior and negative self-labeling, which leads to increased association with drug-using peers. Thus, the social environment (both the peer and familial systems) must be included as a significant focus for intervention to interrupt pathways toward drug use and suicidality. There are also treatments available for working directly with lonely individuals.

Almost one in three suicide attempters in this study had made a repeat attempt. Repeat attempters are increasingly likely to complete their suicides. Respondents in the present study indicate that lethal means are more likely to still be available in the homes of multiple attempters. Since one of five parents of first-time attempters never learned of their child's suicide attempt, it is imperative that families of drugusing attempters be involved in suicide management protocols.

This research has documented that drug-using adolescents who make suicide attempts can be differentiated from both non-drug-using control adolescents and nonattempting drug users. Although sufficient research has been presented to document substance abuse as a significant risk factor for suicide and suicide attempts in adolescence, the full value of our research lies in the further subgroup discrimination of risk factors, ie, between attempter users and controls and between attempter users and nonattempter users. Such comparisons are necessary if we are to refine instruments of assessment for use with high-risk populations.

We believe our results should be viewed cautiously, given their reliance on retrospective questionnaire interviews; nonetheless, they do provide a basis for more refined research studies leading to findings of great applicability to our understanding and treatment of these youths at risk.

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Evaluations of Diapers Containing Absorbent Gelling Material With Conventional Disposable Diapers in Newborn Infants

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• We evaluated 149 infants diapered in either conventional cellulose core disposable diapers or diapers containing cellulose core with absorbent gelling material. The infants were evaluated from 1 day of age to 14 weeks of age for the prevalence and severity of diaper dermatitis. We identified a low prevalence of diaper dermatitis throughout the study period. At 14 weeks of age, we noted that infants in diapers containing absorbent geiling material had significantly less diaper dermatitis than those in conventional disposable diapers. Despite the overall low prevalence of diaper dermatitis in the newborn period, 7 of 204 infants evaluated had small skin erosions in the diaper area noted within the first 4 days of age. Both diaper types were associated with infants with erosions. This surprisingly high incidence of erosions in newborn infants suggests previously undocumented increased skin fragility of full-term infants.

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isposable diapers were available in various areas of the United States for many years before 1963, when the Procter & Gamble Co (Cincinnati, Ohio) introduced Pampers as the first nationally marketed disposable diaper. Since that time, diapering practices have radically changed. Currently, over 15 billion disposable diapers are used annually in the United States. This evolution to disposable diapers has developed to such an extent that an estimated 71% of infants are diapered exclusively in disposable diapers, 22% use cloth or disposable diapers, and only 7% of infants are diapered in only cloth diapers (personal communication, Procter & Gamble market research data, 1986).

Currently three classes of diapers are available for infant care. These include

nondisposable, laundered, cotton diapers; conventional cellulose core disposable diapers; and recently introduced extra-absorbent disposable diapers containing an absorbent gelling material (AGM) within the cellulose core. The nondisposable cotton diaper is generally used as one or two folded cotton cloths covered with waterproof plastic pants. Disposable diapers contain a similar construction among the different types and brands. The inner surface of the disposable diaper consists of a topsheet that comes into contact with the infant's skin. The surface of the topsheet is soft for comfort and to reduce friction damage. In addition, the topsheet keeps the wet inner core from direct contact with the skin. The inner structure or cellulose core of the diaper consists of cellulose pulp that absorbs the moisture from the urine and feces. The AGM diapers contain high molecular weight polymers that form a gel when hydrated, locking the fluid into the fiber core. The AGM diapers from different manufacturers differ from one another in composition. amount, and distribution of the AGM in the cellulose core. The outer surface of the diaper is covered by a waterproof polypropylene or polyethylene material.

We have completed a clinical study in newborn infants comparing conventional diapers with diapers containing AGM. We report the results of this study and review current knowledge about diapers and the pathogenesis of diaper dermatitis.

METHODS

This study was approved by the University of Rochester (NY) Perinatal Research Committee and the Committee on Investigations Involving Human Subjects. Infants were entered only after parental informed consent was obtained. Full-term infants with gestational age between 38 and 42 weeks, and birth weight, length, and head circumference between the 10th and the 90th percentiles were entered into this study. In addition, infants were required to be in apparent good health without evidence of

systemic diseases, skin disorders, skin diseases, or birthmarks in the diaper area. Each infant urinated at least once prior to entry into the study. Parents were instructed to diaper the infants in only the assigned test product after entering into the study and for the first 14 weeks of life. An adequate number of diapers was provided in a plain carton labeled with a code designation. To promote normal diapering practices, parents were not requested to record the number of diapers used or the frequency of diaper changes. Parents were not instructed on infant diet management by the investigators at any time during the study.

Prior to entry into the study, the infants were placed in the standard hospital diaper, which was conventional Pampers. Infants who met the criteria for study entry were. entered within the first 24 hours of life. The infants were assigned to a study group using conventional diapers (Pampers) or AGM diapers (Ultra Pampers, Procter & Gamble Co) based on randomization by sex and diet so that male and female infants were equally distributed between the two test groups and infants being breast-fed and bottle fed were also equally distributed. The diaper area was evaluated by a single physician who was unaware of the diaper assigned. Each infant was evaluated prior to entry into the study (day 1 of study), each day during the hospital stay, and at 2, 6, 10, and 14 weeks of age.

The skin condition of each infant was evaluated using a score of 0 to 4, with 0 being normal skin and 4, severely injured skin.1 The individual infant received an overall subjective score giving a general assessment of the condition of the diaper area skin and scores for each of the six specific body areas (waistband, genitals, buttock, legs, intertriginous, and anal). The specific area rash grade was determined by evaluating each area for six types of lesions (ulceration, scaling, papules, edema, macules, and erythema) and adjusting the grade based on the area that the lesions covered. The genital rash score was evaluated by discounting the injured skin appearances in circumcised males. If the area that the lesions covered was less than 10% of the specific body area, the lesion grade was decreased by 0.5. If the area that the lesions covered was 10% to 50% of the specific body area, the lesion grade was not changed. When the area that the lesions covered was greater than 50% of the specific

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	% Frequency by Day of Evaluation						
Product	1	2	3	14	42	70	98
Diapers with absorbent gelling		_		,			
material	3 (99)	5 (94)	16 (32)‡	27 (96)	16 (85)	18 (80)	11†(76)

*Subjective rash grades greater than or equal to 1.0 are considered clinically significant. Numbers in parentheses indicate numbers of infants evaluated.

†Statistically significant difference (P = .014) from conventional diapers.

‡The number of subjects is less at day 3 because a majority of the infants in the study were discharged after only 2 days in the hospital.

body area, the lesion grade was increased by 0.5. For purposes of analysis the maximum lesion grade for the six types of lesions in a particular area is reported as the area rash grade for that area. In addition, any area that showed an erosion or abrasion was noted and followed up during each subsequent evaluation.

The data were analyzed using Student's t test with P<.05 being statistically significant.² The frequency of subjective rash grades greater than 1.0 was evaluated using the χ^2 test.²

RESULTS

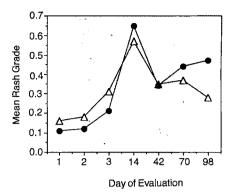
Two hundred four infants entered the study, and 149 completed all 14 weeks of evaluation. By 14 weeks, the overall subjective rash score and each of the six body area rash scores were lower for the AGM diapers than the conventional diapers. The Figure identifies the mean overall subjective rash score throughout the study period and the existence of a statistically significant difference between the two diaper types at the 14week evaluation. Statistically significant differences between the two diaper types were identified at 14 weeks for the waistband (P=.03), genitals (P=.05), and leg (P=.02) rash scores, with the AGM diapers demonstrating lower rash scores. At no other time during the study were statistically significant differences seen between the mean rash grade scores for the two diaper types.

The Table shows the frequency of subjective rash grades greater than or equal to 1.0. A subjective rash grade greater than or equal to 1.0 is considered a clinically significant diaper rash, as at this score or above, mothers consider their infant to have a diaper rash. Of the 149 infants who completed all 14 weeks of the study, 98 different infants had subjective rash grade scores of 1.0

or greater. Forty-seven used the AGM diapers and 51 used the conventional diapers. Fifty-six infants had subjective rash grade scores of 1.0 or greater on one evaluation; 28 infants, on two evaluations; 15, on three evaluations; and 4 infants, on four evaluations. At the 14-week evaluation, the infants diapered in the AGM diapers demonstrated significantly less frequent subjective rash grades greater than or equal to 1.0.

This study enrolled 123 female and 81 male infants. Eighty-seven female and 62 male infants completed the study. At day 1, the mean genital area scores for female infants were 0.47 and 0.51 for those infants that would be wearing the AGM and conventional diapers respectively. The male infant scores were 0.29 and 0.34 for the AGM and conventional diapers, respectively. For both diaper types, the female infants had a significantly higher score (P < .05). This significant difference continued on day 2 for the AGM diaper. Throughout the duration of the evaluations the mean genital rash scores for male and female infants were compared and the scores for female infants were higher than those for male infants at all evaluation dates, but not significantly higher.

To document signs of skin fragility in the newborn, we closely documented and followed up any erosions present in the neonatal period. Seven infants were identified as having erosions in the neonatal period. Three infants were noted to have erosions on the initial day 1 evaluation. Prior to that time, the infants had been in a conventional diaper. Three additional infants had erosions on day 3 and one infant on day 4. One of the infants with an erosion identified on day 3 was diapered in AGM diapers, while the others were in conventional diapers



Average overall subjective rash scores throughout the study for each evaluation day. The day 1 evaluation occurred during the first 24 hours of life prior to starting the test diapers (P = .02 for the 14-week [98-day] evaluation). Circles indicate conventional diaper; triangles, diapers with absorbent gelling material.

at the time the erosion was noted. Each erosion had healed by the day 14 examination.

At 14 days of age, the mean overall subjective rash score and the specific scores for five of the six body areas were higher than at any other time in the study. Also at 14 days, the largest number of infants on both diapers had overall subjective rash grade scores of 1.0 or greater. Despite these higher scores there was no statistical difference between the two diaper types at the day 14 examination. In addition, throughout the study, there was no difference between the scores of the breast-fed and formula-fed infants as a whole or in either diaper.

The Table and Figure do not show data from the fourth and fifth hospital day. These data are not included because of the small number of patients who remained in the hospital for that period. There was no significant difference between diapers during that period of time.

COMMENT

The exact prevalence of diaper dermatitis is unknown but estimates of 7% to 35% of the infant population having diaper rash at any given time have been proposed. ⁴⁶ Several studies have shown that the highest prevalence occurs between 6 and 12 months of age. ^{1,6,7} None of these studies specifically examine the prevalence of diaper dermatitis in the neonatal period. Our studies identified an extremely low mean rash grade for

the overall subjective rash scores in the first 2 days of life. Also, we noted in the specific area scores for the legs, buttocks, genitals, and waistband that the infant scores were higher in the first 2 weeks of life (data not shown). The higher area scores were due to the higher background erythema noted in the initial days after birth. Despite the low prevalence of rash, we were surprised by the number of erosions identified. Three of the erosions were present at the baseline evaluation, suggesting possible trauma associated with labor or delivery. The other four erosions developed during the daily evaluations suggesting recent trauma associated with normal care and handling or secondary to the diapers. Each erosion healed rapidly. To our knowledge, previous documentation of increased skin fragility of full-term infants has not been shown.

The mean overall subjective rash score was lower throughout this entire study than previously reported in infants between the ages of 6 and 12 months.1,3 At day 14, the mean overall subjective rash score was greater than any other time during the study, but there was no statistical difference between the AGM diapers and conventional diapers nor between breast- or bottle-fed infants. The reason for this elevation in both diaper groups at 14 days of age was unknown. Despite the low mean overall subjective rash score, over one half of the infants who completed the study developed clinically significant diaper dermatitis before 14 weeks of age.

The higher incidence of genital rash scores in female infants was interesting. Although this difference was not statistically significant after 2 days of age, it was consistent throughout the study. The cutaneous injury after circumcision was resolved by the 6-week visit and should not have affected the later scores. Perhaps the hyperpigmentation of the male genitalia decreased the observation of erythema and thus lowered the genital scores.

In recent years, new data have clarified the interactions of multiple factors in the pathogenesis of diaper dermatitis. One of the major factors is skin wetness. Moisture from the infant's urine is trapped against the skin where it increases skin wetness. Increased wet-

ness of the skin increases the frictional coefficient of skin and the ease of developing abrasion damage by frictional trauma. The infant's skin suffers frictional injury as the infant moves about within the diaper. When the infant's skin is wet the frictional injury increases. Increased skin wetness also increases skin permeability, allowing more rapid penetration of irritating substances within the diaper environment. In addition, increased skin wetness allows increased growth of microorganisms on the skin.

Leyden et al8 demonstrated that the mean concentration of free ammonia in the morning diaper was the same for infants with or without diaper dermatitis. They also demonstrated that ammonia solutions of higher concentrations than those found in diapers did not cause erythema when applied to adult skin, but the same or lower concentration of ammonia-irritated skin injured by scratches that were deep enough to breach the stratum corneum. Their studies confirmed that ammonia is not the primary cause of diaper dermatitis but it may act as a cofactor by increasing irritation on previously injured skin.

The normal skin pH is in the 4.0 to 5.5 range.11 Occluding skin can elevate the surface pH11 and diaper-occluded skin has a higher pH value than adjacent nonoccluded skin.12 Bacteria that are able to produce ammonia from urea exist on normal skin of diapered infants and skin of infants with diaper dermatitis.8 In addition, feces contain bacterial urease that allows the mixture of urine and feces to release ammonia and elevate the pH.18 Studies using the hairless mouse model for skin irritation demonstrated that elevation of pH has an irritancy effect independent of the presence or absence of ammonia. 13 In diaper dermatitis, the ammonia elevates the skin pH, which induces additional factors to increase irritation of the diapered skin.

Infant feces contain substantial levels of protease and lipase enzymes. Using the hairless mouse model for skin irritation, Buckingham and Berg¹⁴ demonstrated that the proteases and lipases were the major skin irritants in feces of infants. Stool irritancy on skin could be reduced by heating the stool and destroying the enzymes and the irritancy

could be returned by adding back protease and lipase enzymes to the heated stool. The lipases appear to facilitate the proteolytic attack on the skin, and bile salts increase the activity of lipases and can themselves increase existing irritation. All of these irritation effects are increased by elevating the pH that activates these enzymes.¹⁸

The microbiology of diaper dermatitis has been studied in great detail. Diaper materials from cloth diapers, cellulose core diapers, or cellulose core diapers with AGM have little effect on the growth of microorganisms in vitro.15 In addition, the types of diapers do not differ significantly in their ability to promote the growth of microorganisms on skin, to select for any particular organism, or to significantly alter the balance of microflora in the diaper area.15 Quantitative microbiological cultures of the diapered skin of infants with and without diaper dermatitis identified no significant differences between the two except for colonization with Staphylococcus aureus. 16 The S aureus difference was associated with known association of increased prevalence of Saureus with dermatitis and atopic dermatitis. 16,17 The bacteria in the diaper area appear to assist in formation of diaper dermatitis by breaking down urea and elevating the pH. Bacteria do not appear to have a primary role in diaper dermatitis.

The pathogenesis of Candida albicans in diaper dermatitis is not as clear. Candida is associated with diaper rash and is uncommon on nondermatitis skin in the diaper area.16,18 Increased numbers of C albicans organisms in the feces have a strong association with severe rash.1 Ten days of systemic therapy with amoxicillin was associated with a twofold increase in the recovery of C albicans from the rectum and skin in diapered infants. 19 Candida albicans is able to produce a keratinolytic proteinase that can digest human stratum corneum.20 Whether Candida acts as a primary or secondary invader in diaper dermatitis has not been clearly resolved. Candida, when present, can elaborate substances that mediate an inflammatory response and increase the inflammation of the diaper dermatitis skin. 21,22

Previous studies demonstrated that

breast-fed infants have a lower prevalence of moderate and severe rash. The feces from breast-fed infants have lower lipase and protease activity, lower pH values, and lower frequency of measurable urease than feces from infants receiving a formula diet.18 Our study did not identify a significant difference between infants initially formula fed or breast-fed and we did not attempt to promote or modify the infants' diet during the study. Additional studies in the future looking at the pH value of the skin and stool of infants in the first 4 weeks of life may identify the factors associated with the increased prevalence of diaper rash that we observed at 2 weeks of age.

The AGM is a cross-linked sodium polyacrylate that has the ability to absorb many times its own weight of urine. Studies comparing AGM diapers with conventional paper diapers and homelaundered cloth diapers have clearly shown that AGM diapers significantly reduce skin wetness, bring the skin pH values closer to normal, and are associated with significantly less diaper dermatitis. \$1.7.22-25 The effect of the AGM is to tightly hold water and reduce the skin wetness. In addition, the AGM has a pH-buffering capacity that brings the skin back toward normal pH values. \$At

the 14-week visit, our studies demonstrated significantly less diaper dermatitis in the infants wearing the AGM diapers.

Recent reports of oliguria in healthy infants26 and inability to obtain urine from the AGM diaper27 reflects ignorance of the hydrophilic properties of the AGM. The hydrophilic nature of the AGM excludes its use in premature infants in a high-humidity environment where the AGM can absorb moisture from the air and gain weight. If the diaper is weighed to measure urine output, the weight gain suggests that the infant urinated when he or she did not.28 Additional studies suggested that the AGM diaper can be used in the small infant placed under a radiant warmer. The AGM diaper retains the voided urine by decreasing the evaporation losses and giving a more accurate estimate of the urine volume voided.29

The AGM was implicated as causing a clear bead discharge from the vagina of a 4-month-old infant. The AGM was not irritating but its appearance caused concern. Physicians who care for children should be aware of the characteristics, both benefits and disadvantages, of all diaper types available for children. The benefits of decreased skin wetness, which protects infants from diaper der-

matitis, also may limit the ability to recognize when small volumes of urine have been excreted.

Our study identified a statistically significant lower prevalence of diaper dermatitis when comparing AGM diapers with conventional diapers at 14 weeks of age. Prior to that time, the overall prevalence and severity of diaper rash was low and no statistical difference between the two diapers was noted. Future additional studies may clarify the relationship of diaper dermatitis prevalence and severity with the physiological skin maturation that occurs during the neonatal period. The frictional component may be less at different ages. The skin pH and proteolytic enzyme changes may be associated with specific diet changes in addition to those related to breast milk or formula. The frequency of diaper changes may be related to motor and psychosocial child development. Multiple factors change as the infant becomes a toddler, many of which may increase the frequency of diaper dermatitis. Additional future studies will, it is hoped, give additional information about the usefulness of topical creams, lotions, or wipes on the diapered skin.

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Does Breast-feeding Protect the Hypothyroid Infant Whose Condition Is Diagnosed by Newborn Screening?

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• Neuropsychological abilities at 1, 3, 5, and 6 years of age were compared in 107 children with congenital hypothyroidism identified by newborn screening who had been either breast-fed or formula fed during infancy. The thyroxine level was significantly higher in breast-fed children than formula-fed children at 1 and 2 months of age, but the level was not higher later during the first year of life. Controlling for parent IQ, socioeconomic status, and dose level, no differences in overall neuropsychological functioning were observed. Children with ectopic glands showed a significant advantage with breast-feeding on several tasks at 3 years of age. These results signify that thyroxine levels in infancy from breastfeeding are not necessarily reflected in improved intellectual functioning later in childhood.

(AJDC. 1990;144:319-323)

Screening newborns for congenital hypothyrcidism (CH) allows for earlier hormone replacement than was previously possible with clinical diagnosis. However, even with the fastest of screening programs, there is still a delay before treatment is initiated and euthyroidism is achieved. This delay may later be associated with neurocognitive impairment.14 Because breast milk contains small quantities of thyroid hormones not found in commercial formula preparations,5-9 breastfeeding may provide some protective benefit to the hypothyroid infant before treatment can be given, and euthyroidism ultimately achieved.10 Indeed. several cases have been reported of patients whose hypothyroidism only became evident clinically once breast-

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Reprint requests to Psychology Department, Hospital for Sick Children, 555 University Ave, Toronto, Ontario, Canada M5G 1X8 (Dr Rovet). feeding was discontinued.¹¹ Furthermore, a retrospective study involving 51 9- to 15-year-old children with CH diagnosed clinically found that breast-feeding in infancy was associated with better intellectual prognosis than formula feeding.¹² Because higher IQs were correlated with earlier treatment onset in formula-fed (FF) children but not in the breast-fed (BF) children, this was thought to signify that the latter were being protected by breast milk before treatment could be given.¹²

Outcome in children with CH now diagnosed by newborn screening is less optimistic, but the issue has not been adequately resolved. Letarte et al¹³ reported no difference between 12 BF and 33 FF children with CH when they were 1 year of age in either their growth or intellectual development. Similarly, we found no difference in the intelligence of 30 BF and 31 FF children with CH who ranged in age from 1 to 6 years, the majority of whom were below 2 years of age.14 Both studies were restricted, however, by relatively small sample sizes and very young children for whom test instruments are considered less reliable and poor predictors of outcome. Furthermore, few if any deficits have been observed in children with CH diagnosed by screening programs at these young ages.3 In addition, these studies also failed to control for such factors as socioeconomic status (SES) and parental intelligence, which are known to influence the choice of feeding method and intellectual outcome, 16,16 as well as the cause of the hypothyroidism.

We presently report our findings on larger groups of BF and FF children with CH as infants (1 year of age) and later at ages when impairments in neurocognitive function have been documented, namely 3, 5, and 6 years of age. It is hypothesized that if breast

milk s protective, the following should occur: (1) BF children should outperform FF children when family variables (SES and parent IQ) are controlled for; (2) the differences between BF and FF children should be greater at older than at younger ages; (3) the differences should be larger in children who are missing their thyroid gland than in children with causes that allow for some partial thyroid function; and (4) the correlation between poorer outcome and longer delay in treatment onset should be larger for FF and BF children.

SUBJECTS AND METHODS

Th∈ sample consisted of 107 children (32 males) born between 1976 and 1986, who were positively identified as having CH through neonatal thyroid screening programs. 18,19 They represent 94% of all screened patients with CH being treated at the Hospital for Sick Children in Toronto. Canaca. Detailed description of their characteristics are given elsewhere.20 There were 29 children with athyrosis, 31 with dyshormonogenesis usually with goiter, and 47 with ectopic glands. Of the 107 children participating, 85 (46 BF) received the 1-year assessment, 86 (52 BF) received the 3-year assessment, 91 (43 BF) received the 5-year assessment, and 70 (32 BF) received the 6-year assessment.

Procedure

When our study began in 1981, every child with CH whose parents had agreed to participate in the study was seen initially at his or her forthcoming birthday and subsequently on ar annual basis thereafter until age 9 years. Any child born between 1981 and 1986 was also added to the sample and assessed initially at 1 year of age. Sixty-eight children entered the project when they were 12 months of age, 13 entered at 2 years, 11 entered at 3 years, 6 entered at 4 years, 6 entered at 5 years, and 3 entered at 6 years. Children with CH having other congenital anomalies or handicapping conditions were excluded from the study. Although prematu-

rity was not an excluding factor, it was generally rare in our sample. Only 8 children had birth weights below 2500 g and only 2 of these had gestational ages younger than 36 weeks. One other child born at 34 weeks' gestation had a birth weight above 2500 g.

Assessments were conducted at The Hospital for Sick Children by psychometrists who were "blind" to feeding status. Testing of one parent (usually mother) took place at the child's initial assessment. Parents were also interviewed at this time about infant feeding and if the child was BF, the age at which this was discontinued.

Tests

For the 1-year assessment, the children received the Griffiths Scales of Infant Development²¹ and the Reynell Language Scales.²² The Griffiths is a sensitive and widely used measure of infant intellectual development, which, unfortunately, is limited at present by outdated norms that yield somewhat inflated scores.28 (The test is presently being restandardized, but current norms are not yet available.) The Griffiths provides a General Developmental Quotient (mean ± SD, 100 ± 15) as well as developmental quotients on five subscales: locomotor, personal social, hearing and speech, eye-hand coordination, and perceptual performance. The Reynell provides z scores (mean \pm SD, 0 ± 1) on two scales: receptive language and expressive language. Thus, there were eight measures in all for the 1-year assessment.

At the 3-year assessment, children received the Griffiths Scale, the Reynell Language Scale, and the Beery-Buktenica Test of Visual Motor Integration. The latter, which has been standardized for a wide age range, involves copying a series of progressively more complex abstract figures. Percentile equivalents are provided. At this age, the Griffiths Scale includes an additional subscale, verbal reasoning. There were 10 indexes of performance at this age.

At age 5 years, children were assessed with the Wechsler Preschool and Primary Scales of Intelligence, ²⁵ the Beery-Buktenica Test, the Reynell Language Scale, and two subscales of the McCarthy Scales of Children's Abilities, memory and motor. ²⁵ The Wechsler Preschool and Primary Scales of Intelligence, which is a widely used measure of intelligence at this age, provides a full-scale IQ (mean \pm SD, 100 ± 15) and IQ on two subscales, verbal and performance, as well as scaled scores (mean \pm SD, 10 ± 3) on 11 individual subtests. The two McCarthy scales provide t scores (mean \pm SD, 50 ± 10). There were 10 indexes of performance at this age.

At age 6 years, children received the complete McCarthy test, which provides a general cognitive index (mean \pm SD, 100 ± 15) as well as T scores on five subscales, verbal,

perceptual, quantitative, memory, and motor; they also received the Reynell Language Scale and the Beery-Buktenica Test. At this age, neuromotor competence was additionally assessed with the Bruininks-Oseretsky Test of Motor Proficiency²⁷ that provides a percentile equivalent score. There were 10 indexes of performance at this age.

Parent IQ was assessed with the abbreviated Wechsler Adult Intelligence Scale–Revised²⁸ and SES with the Hollingshead Four Factor Index.²⁹ Only full-scale IQs were recorded. The Hollingshead index provides a score based on education and occupation of both parents.

Medical Data

The following information was available on each child: skeletal maturity at diagnosis; cause of hypothyroidism as indicated by technetium scans; the age at the start of treatment; initial dosage; and thyrotropin (TSH), thyroxine (T₄), and triiodothyronine (T₃) levels at diagnosis and at clinic visits throughout the first year. These usually involved monthly visits until age 4 months, and then at ages 6, 9, and 12 months, and annually thereafter. Age at normalization of T, levels was determined by interpolating from the regression between hormone levels and age for each child when the circulating T4 level would have reached 130 nmol/L (see Rovet et al³⁰ for rationale). The study was approved by The Hospital for Sick Children's Human Subjects Review Committee.

RESULTS

Fifty-eight (54%) of the children with CH were BF while 49 were FF. The mean (\pm SD) duration of breast-feeding was 19.5 ± 14.9 weeks (range, 2 weeks to 1 year).

Breast-fed children did not differ from FF children on any factor associated with illness severity. Their mean skeletal ages (weeks of gestation) at diagnosis were 36.6 weeks for BF children and 37.0 weeks for FF children. Screening and confirmation TSH levels were 119.3 mU/L and 129.5 mU/L for BF children and 133.0 mU/L and 135.6 mU/L for FF children. The mean (=SEM) circulating T, levels at diagnosis were 62 ±8 nmol/L for BF children and 73 ± 7 nmol/L for FF children; these values were not significantly different. The T_a levels were 1.9 ± 0.2 nmol/L and 2.2 ± 0.2 nmol/L, respectively. The distribution of BF children in each of the causal categories was 67% for athyrotics, 42% for goiters, and 57% for ectopic glands; a χ^2 test indicated that these were not significantly different (P = .28).

Regarding treatment, the mean $(\pm \mathrm{SD})$ age at initiating replacement therapy was 13.9 ± 5.8 days for BF children and 13.0 ± 6.4 for FF children. Their mean $(\pm \mathrm{SD})$ daily starting doses were 8.22 ± 1.7 mg/kg and 7.48 ± 1.9 mg/kg, respectively, which are significantly different (P<.03). Parental IQ was higher for BF children than for FF children (P<.01), as was SES (P<.01).

Thyroid hormone levels, available from 1 month to 1 year, were analyzed via multivariate t tests using the Bonferroni P correction. For T_4 , the results revealed a significant overall difference (Hotelling's $T^2 = 23.92$; P < .004). Univariate tests indicated that BF children had significantly higher T4 levels than FF children at 1 month (P < .001) and 2 months (P < .001). As can be seen in the Table, the T, levels of BF and FF groups were relatively equivalent by 3 months of age. For T_s, the overall difference was not significant; therefore univariate tests were not computed. As can be seen in the Table, the two groups had similar T, levels at all ages.

For BF children, T₄ levels appeared to be normalized (ie, >130 nmol/L) by about 1 month of age, which is within 2 weeks of starting therapy, whereas for FF children, this did not occur until 2 months of age for children with goiter and ectopic glands, and until 3 months of age for children with athyrosis (Fig 1). It took 27.5 days on average for the T₄ levels of BF children to reach 130 nmol/L compared with 70.8 days for FF children, which is significantly different (P < .01). Figure 2, which presents the T_s levels of BF and FF children according to the causen, shows that all groups had T₃ levels within the normal range³¹ by 1 month of age, except infants with athyrosis who were FF.

Starting dose level, parent IQ, and SES were used as covariates in all subsequent analyses because they differed significantly for BF and FF groups. Given the large number of psychological measures at each age, the results were analyzed by multivariate analyses of covariance using the Bonferroni correction. The results revealed no overall differences in performance between BF and FF children at any of the assessment ages.

Mean (\pm SEM) Thyroxine (T_4) and Triiodothyronine (T_3) Levels of Breast-fed (BF) and Formula-Fed (FF) Children With Congenital Hypothyroidism

		mol/L	T _a , n	mol/L
Age, mo	BF	FF	BF	FF
1	161.4±9.4	110.7 ± 9.4*	2.7±0.2	3.0±0.2
2	169.6 ± 7.8	$128.4 \pm 8.0*$	$\pmb{2.6\pm0.2}$	3.1 ± 0.2
3	173.4 ± 7.5	154.5 ± 7.7	3.0 ± 0.1	3.2 ± 0.3
4	176.6 ± 7.6	172.8 ± 8.2	3.2 ± 0.2	3.0 ± 0.2
6	174.2 ± 13.3	169.0 ± 6.3	3.0 ± 0.1	3.0 ± 0.1
9	163.2±9.8	153.9 ± 6.3	2.8 ± 0.1	3.1 ± 0.2
12	161.5 ± 5.2	121.7 ± 4.5	2.4 ± 0.2	2.8±0.1

^{*}P<.001.

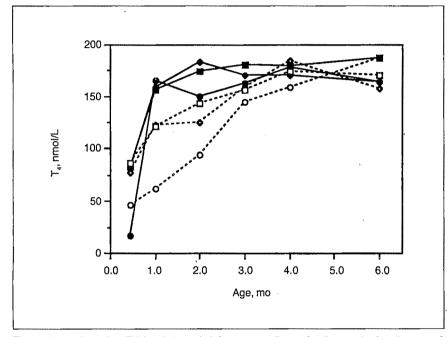


Fig 1.—Mean thyroxine (T_4) levels in early infancy according to feeding method and cause of hypothyroidism. Solid lines indicate breast-fed children; broken lines, formula-fed children; circles, athyrotic causes; diamonds, dyshormonogenetic causes; and squares, ectopic causes.

We next examined whether there were different effects of breast-feeding depending on the cause of the hypothyroidism. This was done by conducting for each assessment age separately, a 2 (feed) \times 3 (cause) multivariate analysis of covariance, using starting dosage, parent IQ, and SES as covariates. The results revealed that for the 3-year assessment, there was a significant omnibus group \times feed interaction (F = 2.19, P < .01; df = 14,497). Univariate tests showed that this reflected primarily general developmental quotient

(F=3.14, P<.05, df=2,71), with marginal contributions of personal social (P<.06), perceptual performance (P<.09), and reasoning (P<.10) scales. Figure 3, which depicts the interaction effect for general developmental quotient, shows that the children with ectopic glands who were BF outperformed all other groups, scoring at a level comparable to that of normal controls, as described previously. Children with ectopic glands who were FF scored similar to children with athyrosis, regardless of type of feeding. A se-

ries of t tests conducted within the ectopic group revealed significantly lower scores by those who were FF on the following scales: personal social (P<.04) and eye coordination (P<.01) at 1 year and locomotor (P<.04), personal social (P<.02), and reasoning (P<.01) at 3 years. There were no comparable effects for the tests given at 5 and 6 years of age.

Hypothesis 4 predicted that if breastfeeding is protective, negative correlations would be observed between outcome variables and age at treatment onset for FF but not for BF children: the difference between the correlation coefficients of the two groups should also be significant. This pattern of results was observed for two variables only, eye-hand coordination skills at 12 months of age (r = -.104 for BF children and -.612, P < .001 for FF children: t = -4.90, P < .001) and neuromotor skills as assessed by the Bruininks-Oseretsky Test of Motor Proficiency²⁷ at age 6 years (r = .076 and -.335, P < .05; t = -2.12, P < .05).

COMMENT

The results revealed that children with CH who received breast milk in early infancy had higher T₄ levels in the first 2 months of life and achieved euthyroidism sooner than did children who were given commercial formula preparations. This, however, was not conferred onto intellectual testing, as children who were in the BF group did not demonstrate any significant overall advantage at any of the four assessment ages from those who were FF. Thus, there is minimal support for the first two hypotheses.

Regarding origin, it was predicted that children with athyrosis would benefit most from breast-feeding because they had the most severe condition and the lowest thyroid hormone levels at the time of treatment onset. Present findings instead showed an advantage of breast-feeding, but only for children with ectopic glands. This was observed primarily at 1 and 3 years of age and in several areas of intellectual functioning. Because the ectopic origin is usually associated with partial thyroid function, this result seems initially counterintuitive. However, recent studies suggest that the ectopic condition is not static

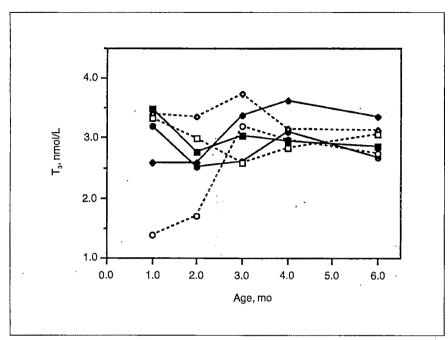


Fig 2. — Mean triiodothyronine (T_a) levels in early infancy according to feeding method and cause of hypothyroidism. Solid lines indicate breast-fed children; broken lines, formula-fed children; circles, athyrotic causes; diamonds, dyshormonogenetic causes; and squares, ectopic causes.

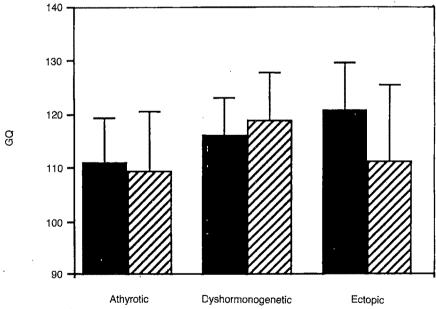


Fig 3.—Griffiths general developmental quotient (GQ) scores of breast-fed (solid bar) and formula-fed (striped bar) children at age 3 years by cause of hypothyroidism.

but rather is on a continuum with the athyrotic condition, with the children with the ectopic condition progressively losing functional capacity after birth. 32 It is possible that supplementary T_4 in

breast milk is adequate for these children as their residues vanish, but it is insufficient for the children who lack thyroid glands. Furthermore, the protective benefit may be too late for chil-

dren with athyrosis because their cognitive deficits appear to be prenatal in origin. 33

There was limited support for the fourth hypothesis that if breast-feeding is beneficial, outcome would be negatively associated with the delay in treatment onset for FF but not BF children, because the latter are being protected during this period. This effect was observed for two indexes only, fine motor skills at the 1-year assessment and neuromotor competence at the 6-year assessment. Because of the large number of comparisons overall (n=48), it is quite reasonable to assume that the two significant effects could also be attributed to chance.

It is not readily clear what the protective mechanism of breast-feeding actually is. Studies of the hormonal constituents of breast milk report low but persistent levels of T3, which only become evident after 1 month of age, but nondetectable levels of T4.834 Furthermore, it is not certain what the effects can be when the levels of T, in breast milk only amount to what represent 25% of the total daily requirement. 5,8 Nevertheless, one might argue that it is not the total amount of hormone that is important but the timing of its presence at a critical stage of neural maturation that is essential.

Besides the benefits from exogenous thyroid hormones in breast milk, this method of feeding has also been shown to impact positively and over the long term on the neurocognitive skills of normal healthy nonhypothyroid children. 13,85,86 There is some thought that this is due to psychological effects as well as to other metabolites unique to breast milk. However, because we did not record the method of feeding in the controls described in our other studies, 20 we have no way of knowing whether the benefits observed presently were due to thyroid hormones in the milk or to these other psychological and metabolic effects. By the same token, one also does not know what produced the advantages reported in the other studies on healthy BF children18 because T4 and other metabolites were not assayed in this research. Clearly, further studies in this area are necessary.

Other limitations of the present work also include the following: (1) our inabil-

ity to control for daily fluctuations in hormone levels; (2) individual sensitivities to thyroid hormone; (3) compliance; (4) incomplete ingestion of administered T_4 ; (5) variations in function of the thyroid gland in the ectopic group; and (6) the reliability of test measures, particularly the infant tests. Unfortunately, as the first five factors are difficult to control, one has to assume that their effects are minimal because they are randomly distributed throughout both feeding groups.

In conclusion, this study has provided minimal support for the hypothesis that

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breast-feeding will protect the hypothyroid infant. Even though breast-feeding was associated with higher T_4 levels during the first 2 months of life, this was not translated into improved cognitive function later. The only group to show any advantage from breast-feeding was children with ectopic glands, but this effect did not persist past 3 years of age. Although the issue of the appropriate starting dose is still a matter of controversy, 37 one practical implication of our findings is that a higher dose level may have to be considered for children who are FF to normalize their T_4 levels at a

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faster rate. Moreover, until the longerterm effects of early breast-feeding have been established, pediatricians should encourage mothers of hypothyroid children who do choose to breastfeed to continue as long as possible, at least until hormone levels have normalized, especially if the gland is ectopic.

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Donna Sorbara, Jeannine Pinnsonneault, and Robert Ehrlich made contributions to this investigation.

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Extra Hospital Stay and Antibiotic Usage With Nosocomial Coagulase-Negative Staphylococcal Bacteremia in Two Neonatal Intensive Care Unit Populations

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• Coagulase-negative staphylococci were the leading cause of nosocomial bacteremia in the neonatal intensive care units of the Brigham and Women's Hospital and Children's Hospital, Boston, Mass, in 1982. To determine the consequences of these nosocomial bacteremias, a cohort study was conducted in which two comparison subjects were matched with each of 38 bacteremic infants by hospital, birth weight within 100 g, and nearest date of discharge. To adjust for duration of stay in the hospital, it was also required that both comparison subjects have survived and remained in the hospital for as long as the time until bacteremia occurred in the bacteremic infant. The average day of onset of bacteremia was the 20th hospital day. Despite having similar birth weights and comparable severity of underlying illness, bacteremic infants remained in the

hospital for an average of 19.8 days longer than the nonbacteremic comparison subjects (77.3 vs 57.5 days). The bacteremic patients received antibiotics for an average of 11.2 more days than the nonbacteremic infants. Vancomycin hydrochloride was given to 20 (52.6%) of the bacteremic patients but only 4 (5.3%) of the comparison patients. All of the comparison subiects and 37 of the 38 Infants with bacteremia survived. Thus, nosocomial bacteremia with coagulase-negative staphylococci is a late complication of hospitalization that occurs in infants who are already relatively long-term survivors. This bacteremia appears to be associated with substantially longer hospital stay and antibiotic therapy but little, if any, excess mortality.

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C oagulase-negative staphylococci have become the most common blood culture isolates in neonatal intensive care units.19 Although nosocomial coagulase-negative staphylococcal bacteremia generally has been regarded as

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a major problem for neonates who are already critically ill, the adverse consequences of these infections have not been defined. We have investigated the effect of nosocomial coagulase-negative staphylococcal bacteremia on antibiotic administration, prolongation of hospital stay, and mortality. Since our previous studies demonstrated that the risk of bacteremia is strongly associated with both birth weight and duration of exposure to the neonatal intensive care unit, 8-10 we have adjusted for these variables in the present investigation.

> **METHODS** Study Population

All infants admitted to the neonatal intensive care units of the Joint Program in Neonatology at the Brigham and Women's Hosrital and Children's Hospital, Boston, Mass, in 1982 were included. Infants with surgical problems were admitted to surgical subspe-

cialty wards and were not included in this study. The names, medical record numbers, birth weights, lengths of stay, and outcomes of hospitalization for the study infants were obtained from a computerized registry maintained by the Joint Program in Neonatology. All admissions to the neonatal intensive care unit at Children's Hospital were transferred from hospitals in neighboring communities, generally within a few hours of birth, whereas infants admitted to the Brigham and Women's Hospital neonatal intensive care unit were nearly all born in that hospital. To calculate duration of hospital stay in the same manner for all infants, lengths of hospital stay were calculated from the date of birth.

Microbiologic Data

Physicians obtained specimens of blood for culture for the usual clinical indications, such as apnea, bradycardia, temperature instability, or feeding difficulties; surveillance blood cultures were not performed. Blood cultures were obtained percutaneously, except for cultures of blood taken through umbilical artery catheters at the time of placement. Cultures were processed in a conventional twobottle broth blood culture system using standard procedures. 11 The collection of microbiologic data has previously been described in detail.8,9

All results of these blood cultures were taken from the original data in logbooks maintained in the hospital microbiology laboratories. Blood cultures that yielded a single morphologic type or species of coagulasenegative Staphylococcus as the sole isolate were taken as evidence of bacteremia with that organism. Only the first positive culture for each individual was counted. Bacteremias that occurred within the first 48 hours of life were not considered nosocomial in origin and were excluded from further analysis. 8-10,12-14 Thus, the analysis of nosocomial bacteremias presented in this study was conducted on all first bacteremias with coagulase-negative staphylococci that occurred after 48 hours of life.

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and Platt), the Department of Medicine (Drs Freeman and Platt), and the Division of Newborn Medicine (Dr Epstein), Brigham and Women's Hospital, Brockton/West Roxbury Veterans Administration Medical Center (Drs Freeman and Smith), and the Divisions of Newborn Medicine (Dr Epstein) and Infectious Diseases (Drs Sidebottom and Goldmann) and the Infection Control Program (Drs Sidebottom and Goldmann), Children's Hospital, Harvard Medical School, and the Department of

Matching Scheme for Cohort Study to Determine Adverse Consequences of Nosocomial Coagulase-Negative Staphylococcal Bacteremia

A cohort study was conducted to determine the duration of antibiotic treatment, prolongation of hospital stay, and excess mortality associated with nosocomial coagulase-negative staphylococcal bacteremia. Two comparison subjects were selected for each bacteremic patient, and the matched triads were compared for various outcomes, such as mortality, duration of hospitalization, and duration of antibiotic therapy. Two nonbacteremic comparison subjects were matched with each patient with bacteremia by hospital, birth weight within 100 g or 10%, and nearest date of discharge. It was also required that both comparison subjects in each triad have survived and remained in hospital at least as long as the time until the day the first positive blood culture was obtained from the bacteremic infant. This day was used as the date of onset of bacteremia in this study.

Modified Matching Scheme for Cohort Study to Determine Expected Mortality

Initially, we noticed that the crude survival rate for the infants with nosocomial bacteremia was remarkably high for a group with such low birth weights. Therefore, a modified version of the above cohort study was conducted to determine the expected mortality for neonates with the same distribution of birth weights who did not experience nosocomial bacteremia. For this modified study, duration of hospital stay was not considered, and the two nonbacteremic comparison subjects were simply matched by hospital, birth weight within 100 g or 10%, and nearest date of discharge.

Comparisons of Bacteremic Infants and the Matched Comparison Subjects for Severity of Underlying Illness

To determine whether comparisons between infants with and without nosocomial coagulase-negative staphylococcal bacteremia might be confounded by differing degrees of severity of underlying illness apart from low birth weight, we also collected data from the medical records of both the bacteremic patients and their matched comparison subjects on exposure to a number of variables related to severity of illness prior to the onset of bacteremia. ^{7,16-18}

Since validated physiologic indexes of severity of illness are not available for newborn infants, we selected representative diagnostic laboratory tests and therapeutic interventions that might serve as proxies, reflect-

Table 1.—Severity of Underlying Illness Prior to Bacteremia

	Neonates With Bacteremia	Comparison Subjects
Gender distribution, % M	56.1	45.5
Laboratory values prior to bacteremia Elevated total white blood cell count, % of subjects	10.5	10.5
Elevated proportion of immature neutrophils, % of subjects	28.9	42.1
Immature neutrophils, maximum %*	19.1	23.3
Depressed platelet count, % of subjects	60.5	53.9
Respiratory indexes prior to bacteremia Endotracheal intubation, % of subjects	73.7	78.9
Mechanical ventilation, % of subjects	71.1	78.9
Fraction of inspired oxygen of 100%, % of subjects	42.1	40.8
Average maximum daily fraction of inspired oxygen, %*	39.0	42.7
No. of days breathing with respirator assistance*†	12.2	8.4
Bacteremia workups and antibiotics prior to bacteremia Previous bacteremia workups with negative results, % of subjects	81.6	73.7
No. of previous bacteremia workups*†	2.1	1.6
Received antibiotics, % of subjects	94.7	89.5
No. of days antibiotics were given*	9.6	7.8

^{*}Average values.

ing the underlying degree of illness. For the period prior to bacteremia these included hematologic parameters 20-22 and measures of the neonate's reliance on respiratory assistance. In addition, we recorded indexes of clinical instability, reflected in the clinician's decision to perform blood culture workups (the number of 48-hour clinical episodes during which blood was obtained for culture) and the decision to initiate and maintain antibiotic therapy. These indexes are listed in Table 1.

Epidemiologic Analysis of Severity of Illness

Each triad, consisting of one bacteremic patient and two matched comparison subjects, formed an individual stratum. Patients were first compared for their severity of illness prior to bacteremia. Mantel-Haenszel procedures for discrete variables in matched data were used for calculating the summary x values for exposure to hematologic parameters, respiratory indexes, and infection-related variables prior to bacteremia (Table 1). 17-19 Continuous variables, such as the number of days of respirator use, number of bacteremia workups, number of days of antibiotic administration prior to bacteremia, and birth weights, were calculated by averaging the numbers for the two comparison subjects within each triad and then subtracting that average value from the number for the bacteremic infant. Each triad of one bacteremic patient and two matched comparison subjects thus yielded one estimate of a numerical scalar difference. The paired differences from each triad were then compared with the distribution of Student's t. 19 Comparisons of variables reported as proportions, including the percentage of inspired oxygen and the proportion of immature to total neutrophils, were carried out in a similar manner, using the angular or arc sine transform for proportions. 19 The angular transform is a standard way to make distributions of proportions (bounded by 0 and 1) into approximately normal distributions, as required for t tests.

Epidemiologic Analysis of Consequences of Nosocomial Bacteremia

Patients were entered into this study on the basis of their exposure to bacteremia and then compared for the outcomes of excess hospital stay, antibiotic administration following bacteremia, and survival. Comparisons of the number of days of antibiotic administration on or after the onset of bacteremia and the number of days of hospitalization were made within triads as described above, and the paired differences

[†]P<.05 by paired t test.

from each triad were compared with the distribution of Student's t values. ¹⁹ The average added stay with bacteremia was calculated individually within hospitals and again with the two hospital populations combined. Summary estimates of the relative probability of survival with nosocomial coagulase-negative staphylococcal bacteremia over strata were calculated using Mantel-Haenszel procedures for matched cohort studies with test-based 95% confidence intervals. ^{17,18}

RESULTS Study Population

In 1982, 882 infants survived and remained in one of the intensive care units for more than 48 hours and thus entered the period of risk for nosocomial infection. Forty-five (5.1%) of these patients experienced nosocomial bacteremia with coagulase-negative staphylococci. There was a strong association of this infection with low birth weight. Since all 7 infants with birth weights under 700 g who also survived for more than 48 hours experienced nosocomial bacteremia with coagulase-negative staphylococci,10 there were no nonbacteremic comparison subjects with similar birth weights and durations of exposure. Therefore, neonates with birth weights less than 700 g had to be excluded from these analyses.

Application of the Matching Schemes

The matching schemes were successfully applied to the 38 remaining infants with bacteremia, so that 38 triads were formed, each triad containing 1 infant with nosocomial coagulase-negative staphylococcal bacteremia and 2 matched comparison subjects.

Comparability of Bacteremic Infants and Matched Comparison Subjects for Severity of Underlying Illness Prior to Bacteremia

A summary of indicators of severity of illness of the infants with nosocomial coagulase-negative staphylococcal bacteremia and their matched comparison subjects is presented in Table 1. All data are from the period prior to the day of onset of bacteremia. Male and female infants were represented about equally in the study population. Hematologic abnormalities occurred in about half of the study subjects. 2012 Of these abnormalities, depressed platelet counts and elevated proportions of immature neutrophils in the differential white blood

Table 2.—Average Birth Weights of Neonates With Nosocomial Coagulase-Negative Staphylococcal Bacteremia and Nonbacteremic Comparison Subjects*

	N4	Birth Weight, g‡			
Hospital†	No. of Triads	Neonates With Bacteremia	Comparison Subjects		
Both	38	1401 ± 978	1423 ± 997		
Children's	12	1499 ± 1102	1505±1118		
Brigham and Women's	26	1355±911	1385 ± 934		

^{*}Comparison subjects were, on average, 22 ± 48 g heavier (P<.05 by paired t test) than the infected patients with whom they were matched. This represented only a 1.6% difference in birth weight.

†There were no significant differences in birth weight between hospitals. ±Values are mean ± SD.

cell counts were the most common, and the values for the comparison subjects were slightly but not significantly more abnormal than those of the bacteremic infants.

About three fourths of the study subjects underwent intubation and mechanical ventilation, and, again, the proportion was slightly but not significantly greater for comparison subjects. Maximum percentage of inspired oxygen requirements were similar in the two groups, but the bacteremic infants who required mechanical ventilation spent, on average, more days receiving ventilator assistance prior to bacteremia (Table 1).

Physicians were clearly concerned that the infants in this study might have had an infection even before bacteremia actually developed. About four fifths of the infants had negative blood culture workups, and the average infant had workups for approximately two clinical episodes of possible infection prior to bacteremia. A slightly greater percentage of bacteremic infants had at least one bacteremia workup, and the infants in this group had, on average, a significantly greater number of bacteremia workups than the nonbacteremic infants.

Approximately 90% of the infants in both groups received antibiotics prior to the day of onset of bacteremia. Antibiotics were administered for an average duration of more than a week prior to the day of bacteremia, which was more than one third of the total number of days the infants spent in intensive care before bacteremia developed. Bacteremic infants had slightly longer antibiotic courses than the comparison subjects prior to the onset of bacteremia.

The birth weights of the infants with nosocomial coagulase-negative staphy-

lococcal bacteremia and their matched comparison subjects are presented in Table 2. The average birth weight of the 38 infants with nosocomial bacteremia was 1401 g, and the average birth weight of the 38 pairs of nonbacteremic comparison infants matched by hospital, birth weight, duration of exposure to hospital, and nearest date of discharge was 1423 g. Individual values for Children's Hospital and Brigham and Women's Hospital are also presented separately in Table 2. There were no significant differences between hospitals, and although the comparison subjects were an average of 22.4 g (less than an ounce) heavier (P < .05) than the bacteremic infants with whom they were matched, this 1.6% difference in birth weight is not clinically meaningful. From these data it is evident that nosocomial bacteremia with coagulasenegative staphylococci occurs in very small infants, but the matching scheme was successful in selecting comparison infants with similarly low birth weights.

In summary, the comparison infants were more likely than those who eventually became bacteremic to have hematologic abnormalities and to require ventilatory assistance. On the other hand, the infants who eventually became bacteremic, once they had undergone intubation, spent more days receiving respirator assistance. They also were slightly more closely followed up with bacteremia workups and received antibiotics slightly more frequently than the comparison subjects prior to the time of bacteremia. Thus, infants in both groups were very premature, small, and severely ill, but there was no clear pattern from these data indicating that one group was more severely ill than the other prior to the time of bacteremia.

Table 3.—Average Hospital Stays for Nonbacteremic Neonatal Comparison Subjects and Added Hospital Stay for Neonates With Bacteremia*

Hospital†	No. of Triads	Total Stay for Comparison Subjects, d‡	Added Stay for Neonates With Bacteremia, d‡§
. Both	38	57.5 ± 29.7	19.8 ± 27.0
Chi dren's	12	60.8 ± 37.4	10.3 ± 14.7
Brigham and Women's	26	56.0 ± 25.4	24.2 ± 30.1

^{*}The average nospital day of onset of nosocomial bacteremia was day 17.9 at Children's Hospital and day 20.9 at Brigham and Women's Hospital. For both hospitals the average day of onset was day 20.0.

†There were no significant differences between hospitals for any of the above durations.

#Values are mean ± SD.

Survival, % of subjects

97.4

On the day of onset of bacteremia, all 38 infants had clinical changes, such as apnea, bradycardia, temperature instability, or feeding difficulties, that resulted in blood culture workups, and all 38 had blood cultures from which coagulase-negative Staphylococcus organisms were isolated. On the corresponding hospital day, only 3 of 76 comparison subjects had clinical findings that led to bacteremia workups, and all of the blood cultures from the comparison subjects were negative.

Prolongation of Hospital Stay With Nosocomial Coagulase-Negative Staphylococcal Bacteremia

The average durations of hospitalization for patients in both study groups, by individual hospital and with the two hospital groups combined, are presented in Table 3. The average hospital stay for nonbacteremic comparison subjects was nearly 2 months, but the average (\pm SD) stay for neonates with nosocomial coagulase-negative staphylococcal bacteremia was 19.8 \pm 27.0 days longer (P<1 \times 10⁻⁴). Thus, nosocomial bacteremia appeared to add about 2½ weeks to a 2-month hospital stay. The average day of onset of the bacteremia

was hospital day 20. There were no significant differences between hospitals.

100.0

Antibiotic Administration for Nosocomial Coagulase-Negative Staphylococcal Bacteremia

The proportions of patients receiving antibiotics starting on the day of bacteremia and the durations of antibiotic administration are presented in Table 4. Most of the patients with nosocomial coagulase-negative staphylococcal bacteremia received antibiotics on and after this day, while only about one fourth of the comparison patients did. Counting from the day of onset of nosocomial bacteremia, the bacteremic patients received antibiotics for an average of 14.8 days, while the comparison patients received antibiotics for an average of only 3.7 days. Thus, the bacteremic neonates received antibiotics for 11.2 ± 12.3 days more than the comparison subjects $(P < 1 \times 10^{-4})$. While none of the study subjects in either group received vancomycin hydrochloride prior to the day of onset of nosocomial coagulase-negative staphylococcal bacteremia, 20 (52.6%) of the 38 bacteremic neonates received vancomycin afterward, while only 4

(5.3%) of the 76 comparison subjects received this drug ($P < 1 \times 10^{-5}$).

Survival With Nosocomial Coagulase-Negative Staphylococcal Bacteremia Among Members of the 38 Triads of Neonates Included in the Study

All of the 76 comparison subjects survived, while 37 of the 38 neonates with nosocomial coagulase-negative staphylococcal bacteremia also survived. The Mantel-Haenszel summary relative probability of survival8 with nosocomial coagulase-negative staphylococcal bacteremia for the matched triads was 0.97 (95% confidence interval, 0.66 to 1.44). indicating no difference in survival between the groups. The lone death occurred in a 1140-g infant who received antibiotics for the first 25 days of his hospitalization, including vancomycin on the day of onset of bacteremia, and then died with an intracranial hemorrhage and progressive hydrocephalus 6 days later.

Expected Survival in a Group of Infants With Similar Birth Weights

We were surprised by the very low mortality in this group of tiny premature infants. Nosocomial coagulasenegative staphylococcal bacteremia is a late event and occurs, on average, after nearly 3 weeks of hospitalization. In contrast, most deaths among neonates occur in the first 48 hours of life, so our original matching criteria, which required equal duration of exposure to hospital prior to bacteremia, selected for comparison subjects who were already long-term survivors. Therefore, we repeated the matching process for the 38 triads, this time ignoring duration of exposure and simply enrolling infants from the same hospital with similar birth weights and nearest dates of discharge. In this new group of matches only 66 (86.8%) of 76 infants survived. This represents the expected survival of a group of infants with similar birth weights admitted to intensive care units in these hospitals. Thus, the mortality among bacteremic infants who survived long enough (48 hours) to enter risk for nosocomial bacteremia was actually lower than would be expected in a group of neonates with similar birth weights admitted to intensive care units in these two hospitals.

[§]The average added stay with bacteremia was significantly greater than 0 days ($P < 1 \times 10^{-4}$ by paired t test).

^{*}P<1 × 10⁻⁵ by Mantel-Haenszel summary χ^2 analysis for matched data.

[†]Average values. The average added duration of antibiotic administration with bacteremia was 11.2 \pm 12.3 days ($P < 1 \times 10^{-4}$ by paired t test).

Survival With Nosocomial Coagulase-Negative Staphylococcal Bacteremia Among Seven Neonates With Birth Weights Less Than 700 g

We also investigated the outcome of hospitalization for the seven neonates with birth weights less than 700 g who experienced nosocomial coagulase-negative staphylococcal bacteremia but for whom no no suitable matches with sufficiently low birth weights could be found. Five of the seven bacteremic neonates with birth weights under 700 g also survived, which is a higher proportion of survivors than we would have expected overall from a group of neonates with such low birth weights.8,10 There is no evidence from these data that nosocomial bacteremia with this organism is a quantitatively measurable cause of excess mortality.

COMMENT

The most striking outcome of this study is the remarkably high survival rate for neonates with nosocomial coagulase-negative staphylococcal bacteremia. Survival among infants with bacteremia was comparable to that experienced by similar infants who were not bacteremic and stayed in the hospital for a similar time. Although past reports are not completely clear on the mortality among neonates with coagulase-negative staphylococcal bacteremia, there is a general belief that this disease is not as serious as some other bacteremias suffered by neonates.14 While there have been reports of severe focal complications and deaths among neonates, there is convincing epidemiologic evidence for a generalized excess mortality with nosocomial coagulase-negative staphylococcal bacteremia in adults.28 Such events have been the rare exception in our experience with neonates in general neonatal intensive care units, but surgical patients were not included in this study, and the role of foreign bodies, especially those implanted surgically, was not investigated.

In our series, nosocomial coagulasenegative staphylococcal bacteremia was a relatively late event in the hospital; it occurred, on average, on the 20th hospital day. By that time the average patient had already been breathing with respirator assistance for about 10 days, had experienced two bacteremia workups, and had received over a week of antibiotic therapy. Coagulase-negative staphylococcal bacteremia appeared to be a marker for infants who were already relatively long-term survivors and, therefore, had been continuously exposed to the diagnostic and supportive procedures that characterize intensive care.

In interpreting these data there is the concern that some positive blood cultures may have been contaminants and did not represent bacteremia. 23-25 Previous studies have used varying criteria for determining which positive blood cultures indicate true invasion of the blood stream. However, when criteria appropriate for neonates have been employed, neonatologists have thought that at least half of the blood cultures positive for coagulase-negative staphylococci actually represented bacteremia.19 In addition, our previous work indicated that a positive blood culture in the setting of neonatal intensive care is far more likely to represent bloodstream invasion than blood culture contamination. Regardless of the precise proportion of infants who had true bacteremia in our intensive care units, it is remarkable that in a setting where there is a low threshold for obtaining blood cultures and where there is appropriate supportive care, virtually all survived.

Although coagulase-negative staphylococcal bacteremia is not a measurable cause of excess mortality among neonates in intensive care units, it does appear to be associated with an average of about 21/2 weeks of extra hospital stay, which represents considerable separation from the parents as well as additional hospital cost. It is possible that an unrecognized confounding variable related to severity of underlying illness prior to bacteremia was responsible for some of this observed excess hospitalization. Unfortunately, none of the available physiologic indicators of severity of illness, such as APACHE II26 and the Computerized Severity Index,27 have been tested for validity in a neonatal intensive care unit population. Therefore, we considered a number of laboratory and clinical parameters used by others28,28 that might serve as proxies for a true physiologic index of severity of illness.

The two most common hematologic abnormalities were an elevated proportion of immature neutrophils in the differential white blood cell count and a depressed platelet count (Table 1).22 For both of these parameters, the values for comparison subjects were more extreme than those for the infants with bacteremia. Most infants in this study were breathing with ventilator assistance. Again, the comparison subjects were more likely to have undergone intubation and mechanical ventilation than the bacteremic infants, although, once they had undergone intubation, the bacteremic infants continued to receive respirator assistance somewhat longer. The dramatic increase in survival of tiny premature infants seen in the last decade in level III intensive care nurseries has been brought about primarily by these advances in respiratory care.8,30 If there was a difference between the bacteremic infants and their matched comparison subjects according to these important therapeutic requirements, the comparison infants appeared to be somewhat more severely ill.

The frequency of bacteremia workups was examined, since blood cultures are performed when neonates display nonspecific signs of clinical instability, such as apnea, bradycardia, temperature instability, or feeding intolerance. Although bacteremia workups have never been tested formally as an index of severity of underlying illness, it is reasonable to assume that physicians are more likely to obtain blood cultures from neonates who appear to be more critically ill. We found that bacteremic infants had workups slightly more frequently prior to the onset of bacteremia. In addition, they received antibiotics slightly more frequently and for a greater number of days during this period.

Taken together, the multiple significance tests on the 14 variables in Tables 1 and 2 appear to reveal only small random differences between the bacteremic infants and their matched comparison subjects and do not suggest substantive differences in severity of underlying illness that could account for the 19.8 extra days of hospital stay associated with bacteremia. In addition, although mortality was one of the outcomes considered in this study, it also may serve as a marker for the severity

of the underlying illness. The nearly identical survival in the two groups, 37 of the 38 bacteremic infants and all 76 comparison subjects, is a further confirmation of the comparability of the two groups.

It was clear that neonatologists in our institutions believed that nosocomial coagulase-negative bacteremia justified a course of antibiotics, since bacteremic infants had, on average, 11.2 more days of antibiotic therapy than their matched comparison subjects. Since these antibiotics generally were administered near

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the midpoint of an infant's stay in the intensive care unit, they may not have resulted directly in the extra days of hospitalization. It is possible that bacteremia represented a clinical setback that ultimately was reflected in a longer hospital stay. In addition, patients with nosocomial coagulase-negative staphylococcal bacteremia were much more likely to receive vancomycin, an expensive and toxic antibiotic. Vancomycin was prescribed because of the growing awareness that there was a high prevalence of methicillin resistance among

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nosocomial strains of coagulase-negative staphylococci at both hospitals during the time of the study.

Substantial prolongation of hospitalization and excess hospital costs were associated with nosocomial coagulasenegative staphylococcal bacteremia among neonates requiring intensive care. Further investigation of the causes of nosocomial bacteremia with this organism, especially the relation to foreign bodies, ^{32,32} is essential to formulate realistic and effective preventive policies.

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Medical Evaluation of Abused and Neglected Children

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· Children who have been abused and neglected may have a variety of medical problems not apparent to a social worker or other nonmedical professional investigating the allegations. A joint project between a state child protective agency and an urban teaching hospital was undertaken to provide for the systematic medical screening of all children brought to the agency before their placement in foster care. These children received a complete medical evaluation with emphasis on documenting the abuse and neglect and also were screened for other medical problems. A total of 5181 children were evaluated. Forty-four percent of these children had some medical problem, including anemia, otitis media, sexually transmitted infections, and lead poisoning. Additional Instances of abuse and neglect were identified and documented. This systematic evaluation allows for the optimal identification, documentation, and treatment of abuse, neglect, and other medical problems that may affect a child's outcome and adaptation

(AJDC, 1990;144:330-334)

Child abuse and neglect continue to be major social and medical problems in the United States. As many as 1.5 million children a year are estimated to be victims of abuse or neglect.1 The number of reports of abuse and neglect to child welfare agencies increased 66% between 1980 and 1986. In 1987 Illinois reported 91 723 cases of suspected child abuse or neglect, representing a 30% increase in reports since the previous year.2 Three fourths of these children were abused or neglected by their natural parents; two thirds were 9 years or vounger. Seven percent were taken into protective custody, ie, removed from their home because the child appeared to be in some imminent danger. Subsequent to abuse and neglect, about 500 000 children nationally reside in fos-

Children reported to have been abused or neglected are in need of a

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careful and thorough diagnostic assessment, including a present, past, and developmental history, a physical examination, and laboratory screening for common problems. Since, in most states, child protective workers and other nonmedical professionals conduct child abuse and neglect investigations. they may not involve a physician in this evaluation. This absence of medical input may obscure the diagnosis of associated medical problems and, therefore, be insufficient to remove the risk of further abuse and neglect. The reporting of an abused/neglected child represents an opportunity for the pediatrician to plan preventive strategies and treatment programs that address the comprehensive care of this at-risk population.

In 1987 the Committee on Early Childhood Adoption and Dependent Care of the American Academy of Pediatrics3 recommended that all children entering foster care receive medical evaluations. They also recommended that these evaluations be done by physicians familiar with the foster care system and the specific needs of these children. Prior to that time in Illinois, some children sent to foster homes after a caseworker evaluation were later found to have old injuries. It could not be determined if these injuries were caused by the biological parents or the foster parents. In addition, foster parents complained that they were asked to accept children without any information about their medical conditions. Children with contagious diseases were placed in foster homes, thereby exposing entire families to these diseases. A large number of children suffered emotional and psychological sequelae that made proper placement difficult. The failure to recognize such problems resulted in lengthy delays in treatment and subsequently more recalcitrant problems.

To rectify these problems, the state child protective agency, the Department of Children and Family Services (DCFS), and Columbus Hospital, an urban teaching hospital in Chicago, Ill, developed a joint program to provide for the medical screening of all children taken into protective custody because of suspected abuse or neglect. These children were evaluated before a decision was made either to send the child back to the parent(s) or to place the child in foster care.

PATIENTS AND METHODS

A group of pediatricians screened all children taken into protective custody using protocols specific to their ages and particular history of abuse and neglect. All children received a complete physical evaluation; any medical history available was reviewed. Height, weight, and head circumference for any child younger than 2 years were plotted on growth charts. The child's presenting condition—his general affect, hygiene, and level of consciousness—were noted specifically. All signs of physical injuries were documented and noted on body charts.

A complete blood cell count, urinalysis, and tuberculin test were performed on all children. Black and Hispanic children of Puerto Rican descent were screened for sickle cell disease. Urine specimens were obtained for bacterial culture on all girls older than 3 years. Children younger than 5 years were screened for lead poisoning. A gynecological evaluation was performed for all postpubertal girls with a complaint of dysmenorrhea, vaginal discharge, or amenorrhea. Specimens of cervical secretions were obtained in an effort to identify Neisseria gonorrhoeae, Chlamydia trachomatis, and other sexually transmitted diseases. All other sexually active girls received a Papanicolaou smear every 6 months. Urethral specimens were cultured for N gonorrhoeae and C trachomatis in all boys with a urethral discharge, dysuria, or pyuria. Rectal, throat, and vaginal cultures were taken from children who were suspected to have been sexually abused. Bone scans and selected roentgenography were performed on children with suspected physical abuse. An ophthalmologist evaluated children younger than 3 years who had suspected physical abuse and all older children with abnormal eye examination results or a history of eye trauma.

Infants whose mothers had a history of intravenous drug use or multiple sexual partners were screened for hepatitis B antigen and antibody, and for human immunodeficiency virus antibody. In compliance with state law, written consent was obtained from the patient or legal guardian when it was required.

Anemia was defined as a hemoglobin level less than 2 SDs from the normal mean for age and a mean corpuscular volume less than 70 fL added to the age. A urinary tract infection was diagnosed if 100 000 colonies per milliliter of a single organism grew in a clean voided urine specimen. If multiple organisms were present, the cultures were repeated.

Children were diagnosed as having fetal alcohol syndrome if they were growth retarded and developmentally delayed and demonstrated characteristic dysmorphic features. These facial features included ptosis, a thin upper lip, strabismus, upslanted eyes, and a smooth philtrum. Other dysmorphic features, such as hand anomalies, heart murmurs, and scoliosis, were also used in establishing the diagnosis of fetal alcohol syndrome.

The examining physician initially screened for speech and developmental delays by observing the child's personal and social interactions and language and motor skills during the examination. If delays were suspected, the pediatric occupational therapist and pediatric speech therapist performed more extensive formal standardized tests. Some of these tests included the Denver Development Screening Test, the Developmental Test of Visual-Motor Integration by Berry and Buktenica,5 the Brazelton Neonatal Assessment Scale. the Milani-Comparetti Motor Development Screening Test, the Peabody Picture Vocabulary Test,8 the Pre-School Language Scale, and the Illinois Test of Psycholinguistic Abilities. 10

Most children were evaluated and managed as outpatients. Children who were judged to need a more extensive evaluation or intensive medical treatment were admitted. All children with

Table 1.—Medical Problems Identified (N=5181)

table 1.—IMedical Flobletins identified (IV—3101)							
	No. of Positive	Percent of Total					
Medical Problem	Findings	Patients*					
Hematologic							
Anemia	681	13					
Positive sickle cell screen	195	3					
Sickle cell trait	14	NS					
Sickle cell disease ·	, 3	NS					
Thalassemia minor	3	NS					
Thrombocytopenia	2	NS					
Hemoglobin AG disease	1	NS					
Total	899	17					
Urinary Tract Proteinuria	251	4					
Hematuria	204	3					
Pyuria	89	1					
Urinary tract infections	66	1					
Suspected urinary tract infections	53	1					
Other	10	NS ·					
Total	673	13					
Infections	**						
Otitis media	119	2					
Gardnerella vaginitis	85	2					
Chlamydia	48	1					
Gastrcenteritis	48	1					
Gonorrhea	45	1					
Other	45	1					
Streptococcal pharyngitis	44	1					
Conjunctivitis	32	1					
Trichomonas	27	NS					
Pneumonia	5	NS					
Syphilis	3	NS					
Tuberculosis	1	NS					
Other	45	1					
Total.	502	10					
Other		A W					
Heart murmur, cardiac arrhythmias, and hypertension	57	1					
Asthma	13	NS					

^{*}NS indicates not significant.

failure to thrive were admitted and fed an appropriate diet for their ages, and their growth was monitored. These were all children whom DCFS had determined would be at risk for further harm if they remained in their own home during this evaluation. Children younger than 1 year who were exposed to cocaine in utero were admitted and evaluated for infantile apnea and intracranial and renal defects. Ultrasonography of the head and kidneys were done on all of these infants. Serologic study for hepatitis B was ordered to rule out perinatal transmission of hepatatis B. These cocaine-exposed infants were also monitored for apnea and bradycardia during this hospitalization. Other children presenting with acute and chronic medical conditions were treated appropriately.

After the evaluation was completed, a letter was sent with the patient to the next caretaker describing the patient's medical condition, the evaluation done, the medication prescribed, and the recommended follow-up treatment. Although these caretakers were invited to return to this hospital for the children's necessary follow-up care, they were given the option of using physicians or clinics more convenient to their homes.

Children in custody of DCFS were also evaluated when they were moved from one placement to another. Adolescents who had run away from a previous home were examined before they were placed in another home. As a result, some children were seen more than once during the study period. A log was kept of all evaluations, including preexisting medical conditions and problems identified on the examination. These logs from the first 22 months of this study were reviewed and analyzed. The adolescent visits for the first 14 months of the center's operations were reviewed separately.

RESULTS

During this 22-month period, 5181 children were evaluated. Most were evaluated as outpatients: only 431 (8.3%) were admitted for evaluation and treatment. These children were brought to the evaluation center by child protective workers or the police. They had been removed from their homes for a variety of reasons. Only half of these children had been taken into protective custody because of suspected abuse or neglect. Thirty percent came because of neglect, 8% for physical abuse, 3% for sexual abuse, and another 3% of these children were removed because DCFS judged them to be at risk for harm if they remained in their present homes. A number of adolescents (12%) had run away from their homes or previous foster placements. Of the remaining children, 23% were foster children being moved to a different placement setting. The other 21% needed foster care placement because their parents were dead, homeless, physically disabled, or emotionally unable to care for their children; these parents voluntarily sought placement by DCFS for their children.

Forty-four percent of these children were found to have some health problems (Table 1). Hematological problems were the most common. Thirteen percent of the children were anemic, mostly secondary to iron deficiency. In the adolescent population, anemia was more common in girls (13%) than in boys (4%) (Table 2). A large number of children had positive screening test results for sickle cell anemia. Three children were found to have sickle cell disease. One child had hemoglobin AG disease, a rare

Medical Problem	No. of Positive Findings	Percent of Adolescents
Female	639	56*
Male	505	44*
Anemia Female	83	13
Male .	21	4
. Total .	104	9*
Urinary tract infections Female	19	3
Male	0	0
Sexually transmitted diseases, female adolescents Gonorrhea	15	.2
Chlamydia	14	2
Trichomonas	11	2
Gardnerella vaginalis	22	3
Yeast	31	5
Gynecological problems, female adolescents Pregnancy	44	7
Abnormal Papanicolaou smear	17	3
Condyloma accuminata	4	0.6
Carcinoma in situ	2	0.3
Pubic lice	2	0.3

*This total applies to the entire population of adolescents, not the total number of adolescents of the same sex.

hemoglobinopathy causing anemia.

Urinary tract problems were the next most common abnormalities identified. Proteinuria and hematuria were seen in 4% and 3% of the patients, respectively. Although urine cultures were obtained only in girls 3 years and older, 1.3% of the total sample had urinary tract infections. Three percent of the female adolescents had urinary tract infections. An additional 1% were suspected of having urinary tract infections because of abnormal urinalysis results. Also, several children were coincidentally found to have asymptomatic renal anomalies following bone scans performed to evaluate suspected physical abuse. Three children were found to have single kidneys and one child had a horseshoe kidney.

Infectious diseases, including urinary tract infections, were found in 10% of the total sample. One hundred nineteen children (2.3%) were found to have otitis media. Forty-four children (0.8%) had streptococcal pharyngitis, 32 (2.6%) had conjunctivitis, and 5 had pneumonia. The most serious infection identified was meningococcal meningitis in a 1-year-old girl. This child was brought to the center for placement because her mother had left her with a babysitter 2

days before and had not returned. She was immediately recognized to be seriously ill and was evaluated and treated appropriately.

A number of children presented with symptoms of gastroenteritis. Stool specimens were submitted for culture when the physician suspected a bacterial or a rotavirus infection. Ten children had shigella, five had salmonella, and five had rotavirus infections. No children were identified to have Campylobacter jejuni or Yersinia enterocolitica infections.

Heart murmurs were identified in a number of children, although most were functional. One child was found to have congenital heart block. His condition had been previously identifed, but because of parental neglect it had never been completely evaluated and treated. This evaluation was subsequently expedited and completed. One child had severe hypertension; his blood pressure returned to normal when his asthma was treated.

A number of children had medical problems probably related to their impoverished, neglected environments (Table 3). Forty-three children (0.8%) had lead poisoning. All were class II or class III; none were class IV. No child

had symptoms compatible with lead toxicity. This diagnosis was based on 1985 classifications of the Centers for Disease Control, Atlanta, Ga, using blood lead and zinc protoporphyrin levels to designate risk classification of asymptomatic children with elevated lead levels. Head lice and scabies were found occasionally; 13 children were treated for lice and 3 for scabies.

Other medical conditions were identified that required treatment or followup, including neurofibromatosis in 5 children. Inguinal hernias in 5 children and cryptorchidism in 1 child were surgically corrected. Of 414 patients evaluated for suspected physical abuse, 55% had some fresh bruises, abrasions, lacerations, and/or old scars consistent with the allegations of physical abuse. Even more important, 19 patients (4.6%) were found to have fractures not suspected on the physical examination, but identified only by bone scan or roentgenography. Three percent of the children had burns in various stages of healing. Two patients had corneal abrasions. No patients were found to have retinal hemorrhages. Other eve problems were found but appeared to be related to congenital disease rather than physical abuse: 2 children had cataracts. 1 child had optic atrophy, and 2 children with ptosis had fetal alcohol syndrome. Six children had untreated strabismus.

A number of infants were evaluated for sequelae of intrauterine exposure to cocaine. One had hydronephrosis and one had a porencephalic cyst. Five children, all offspring of drug-abusing mothers and/or fathers, tested positive for the human immunodeficiency virus. A number of these children were also found to have hepatitis B exposure, possible toxoplasmosis, and possible cytomegalovirus infections (Table 3). Six children were identified to have dvsmorphic features characteristic of fetal alcohol syndrome. This figure is probably low because the diagnosis depends on recognizing certain phenotypical characteristics. As Graham et al11 demonstrated, using these criteria, only a certain percentage of these children will be identified. The fetal alcohol effects may be more apparent in the child older than 4 years than in the neonate.

Thirty-four children were found to have nonorganic failure to thrive after a thorough inpatient assessment to rule out other causes. Many of these children (16/34 [47%]) were also developmentally delayed. Nineteen percent (6/34) of these children also had speech delays. Of the other children brought to the evaluation center for a variety of reasons, 8 were found to be developmentally delayed and 11 had significant speech delays.

The adolescents presented with a set of problems unique to their age group (Table 2). Sexually transmitted diseases were seen in 1% of the total sample. They were identified commonly in the girls and rarely in the boys. Of 639 female adolescents 15 (2.3%) were found to have gonorrhea, 14 (2.2%) had C trachomatis infection, 11 (1.7%) had trichomonas vaginitis, and 22 (3.4%) had Gardnerella vaginalis infections. Forty-four (6.8%) of the girls were pregnant. Four (0.6%) girls had condyloma accuminata infection. Two (0.3%) had carcinoma in situ and 2 (0.3%) had pubic lice. One pregnant adolescent was found to have syphilis. One male adolescent had positive rapid plasma reagin card test and fluorescent treponemal antibody absorption test results, but had been previously treated.

COMMENT

This study represents the first report of a large-scale effort to systematically evaluate children with suspected abuse and neglect. Hochstadt et al12 evaluated a small group of children (n = 141) entering foster care. They found that these children had a high incidence of medical problems and recommended that the evaluation effort be expanded and regionalized. This large study demonstrates the need for a complete medical assessment as recommended by the American Academy of Pediatrics Committee on Early Childhood Adoption and Dependent Care.3 These children have a large number of unidentified medical problems. Problems such as anemia and sexually transmitted disease are seen more commonly in this group than in other children of similar ages. The overall evidence of anemia in our group was 13% compared with the 2.4% to 2.8% incidence in children in Minneapolis.18 Among the female adolescents, 13% of our group were anemic vs 8% of female adolescents in a general population.14 The differences among the male adolescents were not as dramatic.

Table 3.—Medical Conditions Directly Related to Abuse and Neglect

Condition	No. of Occurrences
Physical abuse	
Multiple abrasions,	
ecchymoses, and/or	
scars	138
Unsuspected old/new .	
fractures	19
Suspected sexual abuse	17
Burns, old or new	14
Human bite	2
Corneal abrasion	2
Maternal drug/alcohol abuse	,
Intrauterine exposure to	
cocaine	40
Hydronephrosis	1
Proencephalic cyst	1
Fetal alcohol syndrome	6
Human immunodeficiency	
virus positive	5
Hepatitis B	3
Possible toxoplasmosis	2
Neglect	
Lead poisoning	43
Failure to thrive	34
Developmental delay	24
Head lice	13
Speech delay	17
Tinea corporis	10
Scabies	3
Rat bite	1

with 4% in our group being anemic compared with 3% nationally. Gonorrhea was seen in 2% of patients in this group compared with 1% in other adolescents nationally. ¹⁴

The initial evaluation assists in documenting the chronicity and severity of physical abuse. A number of children were found to have fractures not readily apparent on physical examination. These findings ultimately assisted child welfare workers and the judicial system to plan better home interventions. treatment, and placement of these children. Jaudes15 found that the presence of fractures strongly influenced judges; children with fractures were much more likely to be sent to foster homes than returned to their own homes. These data demonstrate the importance of a systematic evaluation.

A method of ensuring that foster parents receive some medical information and access to follow-up care is also demonstrated by this project. A chronic complaint of foster parents in other states is that they receive little or no medical information about a foster child. Eighty percent of foster parents in California reported that they receive inadequate medical information on children entrusted to their care. Although we did not assess how well foster par-

ents and biological parents followed up on our recommendations for further diagnostic procedures and treatment, Hochstadt¹⁷ found that parents followed up on a large percentage of recommendations made by a similar multidisciplinary team.

We believe that this evaluation method should also help to improve the overall provision of medical care to children in foster care. These children have been reported to have more acute and chronic problems than their peers. 18,19 Presumably, many of these problems existed before the child entered foster care. Once they enter foster care, medical care is often fragmented or nonexistent. Swire and Kavaler²⁰ found that children in foster care were inadequately immunized and often not screened for problems common to their age group and that physician records were incomplete. There was little follow-up on problems that were identified. Schor²¹ also found that the level of medical care given to children in foster care was poor. Foster parents were given inadequate medical information. Their responsibility to follow-up on medical care was poorly defined.

The limitations to this evaluation model should be noted so that future evaluation programs can be improved. Since there was generally little or no medical history available at the time of the evaluation, this information could not be used in the examination or passed on to foster parents. We are currently working with DCFS to develop an information questionnaire for child welfare workers to administer to parents during their investigation. Information about immunizations, previous serious illnesses, medications, allergies, and names of medical care providers would be obtained. This information would remain in a child's permanent medical file and be relayed to foster parents.

Because these children arrived 24 hours a day and had to be evaluated as they presented, screening for mental health problems was very limited. The only history available was what the child could report. When examinations were performed in the middle of the night, as happened frequently, the children were tired and often hungry. They could not be subjected to even such screening tests as the Vineland Adaptive Behavior Scale or the Louisville Behavior Checklist used by Hochstadt and Jaudes12 in their evaluations. However, it is suspected that a large number of these children had some psychological or behavioral problems based on the reports of other investigators. 12,19 Children who needed to be hospitalized were evaluated more extensively and often were found to have school difficulties, depression, adjustment disorders, and other mental health problems. Clearly, child mental health screening methods and/or instruments need to be developed for use in this population.

Developmental assessment was severely limited due to the lack of documentation of the child's history. Sometimes even the child's correct birth date was not known if he or she was abandoned by the parent. Again, there was usually no history of milestones or birth history. Children who were tired and hungry could not be expected to fully cooperate with any screening procedure. Children who were admitted to the hospital did receive a more thorough examination under more optimal conditions. Many delays in speech and development were identified in this group.

The state of Illinois has now opened a shelter for short-term care at the same site as the medical clinic. This allows for the examination of children during daytime hours after they have eaten, rested, and adjusted to their surroundings. An occupational therapist is now onsite and screens all children younger than 6 years. We anticipate that this will allow for more thorough developmental screening. Mental health screening and diagnostic assessments will also be added in this new format.

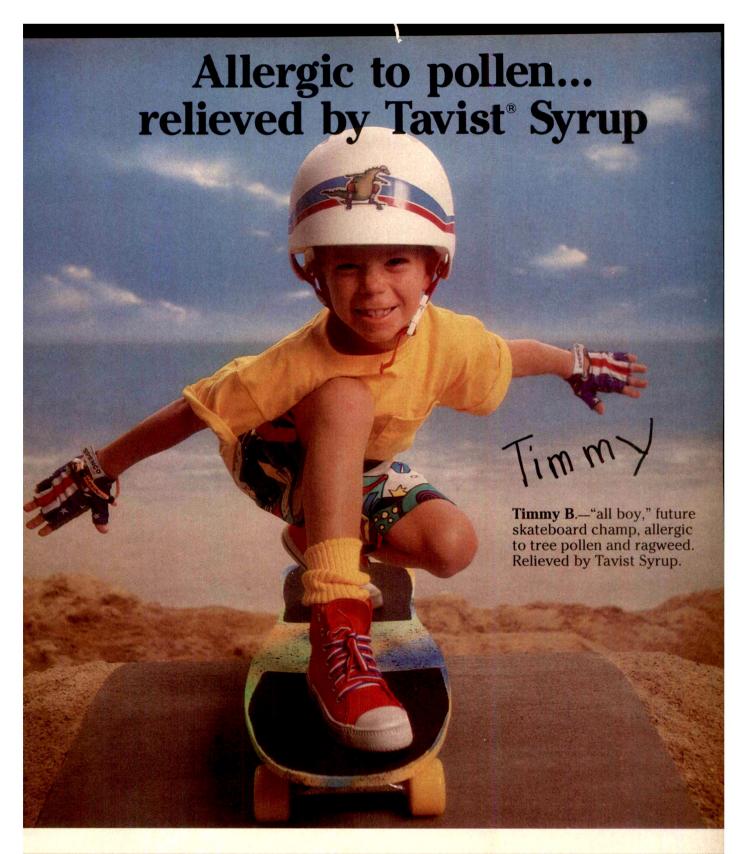
CONCLUSION

Assessment and treatment of children taken into protective custody can be an overwhelming task that invites a sense of hopelessness in those involved in this work. Medical professionals respensible for these children's welfare must organize systems to create order.

The program described here demonstrates one model for providing a comprehensive medical evaluation to all children prior to their placement in foster care as recommended by the American Academy of Pediatrics. The results of this study document the need and utility of such an assessment. This complete medical evaluation helps to identify and document the evidence of abuse and neglect. It assists foster parents in providing necessary medical care and follow-up intervention. This particular program presents one model that allows the medical community, child protective agencies, and the courts to work together for more effective intervention and treatment for abused and neglected children.

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INDICATIONS AND USAGE: Nix is indicated for the single-application treatment of infestation with *Pediculus humanus* var. *capitis* (the head louse) and its nits (eggs). Retreatment for recurrences is required in less than 1% of patients since the ovicidal activity may be supplemented by residual persistence in the hair. If live lice are observed after at least seven days following the initial application, a second application can be given.

CONTRAINDICATIONS: Nix is contraindicated in patients with known hypersensitivity to any of its components, to any synthetic pyrethroid or pyrethrin, or to chrysanthemums.

WARNING: If hypersensitivity to Nix occurs, discontinue use.

PRECAUTIONS:

General: Head lice infestation is often accompanied by pruritus, erythema, and edema. Treatment with Nix may temporarily exacerbate these conditions.

Information for Patients: Patients with head lice should be advised that itching, redness, or swelling of the scalp may occur after application of Nix. If irritation persists, they should conswith their physician. Nix is not irritating to the eyes; however, patients should be advised to avoid contact with eyes during application and to flush with water immediately if Nix gets in the eyes. In order to prevent accidental ingestion by children, the remaining contents of Nix should be discarded after use.

Combing of nits following treatment with Nix is not necessary for effective treatment. However, patients may do so for cosmetic or other reasons. The nits are easily combed from the hair treated with Nix after drying.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Six carcinogenicity bioassays were evaluated with permethrin, three each in rats and mice. No tumorigenicity was seen in the rat studies. However, species-specific increases in pulmonary adenomas, a common benign tumor of mice of high spontaneous background incidence, were seen in the three mouse studies. In one of these studies there was an increased incidence of pulmonary alveolar-cell carcinomas and benign liver adenomas only in female mice when permethrin was given in their food at a concentration of 5000 ppm. Mutagenicity assays, which give useful correlative data for interpreting results from carcinogenicity bioassays in rodents, were negative. Permethrin showed no evidence of mutagenic potential in a battery of *in vitro* and *in vivo* genetic toxicity studies. Permethrin did not have any adverse effect on reproductive function at a dose of 180 mg/kg/day orally in a three-generation rat study.

Pregnancy: Teratogenic Effects: Pregnancy Category B: Reproduction studies have been performed in mice, rats, and rabbits (200-400 mg/kg/day orally) and have revealed no evidence of impaired fertility or harm to the fetus due to permethrin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the evidence for tumorigenic potential of permethrin in animal studies, consideration should be given to discontinuing nursing temporarily or withholding the drug while the mother is nursing

Pediatric Use: Nix is safe and effective in children two years of age and older. Safety and effectiveness in children less than two years of age have not been established.

ADVERSE REACTIONS: The most frequent adverse reaction to Nix is pruritus. This is usually aconsequence of head lice infestation itself, but may be temporarily aggravated following treatment with Nix. 5.9% of patients in clinical studies experienced mild temporary itching; 3.4% experienced mild transient burning/stinging, tingling, numbness, or scalp discomfort; and 2.1% experienced mild transient erythema, edema, or rash of the scalp.

DOSAGE AND ADMINISTRATION:

Adults and Children: Nix is intended for use after the hair has been washed with shampoo, rinsed with water and towel dried. Apply a sufficient volume of Nix to saturate the hair and scalp (especially behind the ears and on nape of the neck). Nix should remain on the hair for 10 minutes before being rinsed off with water. A single treatment is sufficient to eliminate head lice infestation. Combing of nits is not required for therapeutic efficacy, but may be done for executive statement and provided. cosmetic reasons or to meet school 'no nit' policies. A nit comb is provided.

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Special Features

Radiological Cases of the Month

William F. Coughlin, MD; Richard T. Harper, MD; Richard Hatch, MD (Contributors);
Beverly P. Wood, MD (Section Editor)

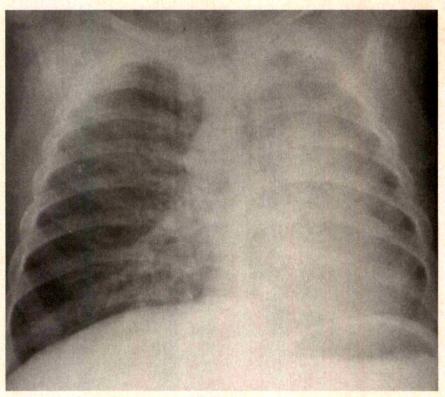


Figure 1.

Accepted for publication May 26, 1989. Contributed from the Departments of Radiology (Drs Coughlin and Harper) and Pediatrics (Dr Hatch), Tripler Army Medical Center, Hon-

olulu, Hawaii.

Reprint requests to the Department of Radiology, Childrens Hospital of Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90027 (Dr Wood).

An 11-month-old boy came to medical attention after a heart murmur was detected during a routine physical examination. He was referred to our institution for evaluation of abnormal chest roentgenographic findings (Fig 1). The pregnancy and perinatal course

were normal and the patient had no history of cyanosis or serious child-hood illness. At presentation the boy had developed normally and was active and acyanotic. A ventilation-perfusion scan (Fig 2) and a right ventriculogram (Fig 3) were obtained.

The Editors welcome contributions to Picture of the Month and Radiological Case of the Month. Those who wish to contribute should send their manuscripts to Dr Feingold (Picture of the Month), National Birth Defects Center, Franciscan Children's Hospital, 30 Warren St, Brighton, MA 02135, or Dr Wood (Radiological Case of the Month), Department of Radiology, Childrens Hospital of Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90027. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.

Denouement and Discussion

Congenital Complete Absence of the Left Pulmonary Artery and Hypoplastic Left Lung

Fig 1.—Posteroanterior chest roentgenogram shows a small left hemithorax, shift of the mediastinum to the left, and diminished pulmonary vasculature in the left lung.

Fig 2.—Top, Posterior image from a xenon 133 ventilation scan shows decreased ventilation of the left lung. Bottom, Anterior image from a technetium Tc99m macroaggregated albumin perfusion scan demonstrates no activity in the left lung.

Fig 3.—A right ventriculogram confirms the absence of the left pulmonary artery.

Unilateral absence of a pulmonary artery is a rare congenital anomaly that affects the right pulmonary artery more commonly than the left.1 Typically, the absent artery is on the side opposite to the aortic arch. This is diagnostically important since the presence of a left arch and an absent right pulmonary artery is rarely associated with congenital heart disease1 and is the most frequent isolated anomaly. There is an 80% incidence of congenital heart disease in those patients with absence of the left pulmonary artery.2 Tetralogy of Fallot is the most common underlying cardiac anomaly in patients with absence of the left pulmonary artery, and it is this condition that brings such patients to medical attention at an earlier age than those patients who have absence of the right pulmonary artery.

The chest roentgenogram usually shows decreased lung volume on the side of the pulmonary artery anomaly and compensatory hyperinflation of the contralateral lung. The mediastinal contents are shifted toward the smaller hemithorax and there is decreased or abnormal-appearing pulmonary vasculature in the affected lung.

In addition to the absence of a pulmonary artery, the differential diagnosis of a unilateral small lung includes congenital pulmonary artery hypoplasia and the Swyer-James-MacLeod syndrome. The absence of air trapping on an expiratory chest roentgenogram will militate against the Swyer-James-MacLeod syndrome, and a ventilation-perfusion isotope lung scan can be

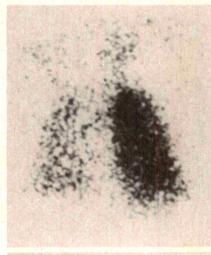




Figure 2.

diagnostic (Fig 2). Air trapping on the ventilation portion of the study will be present in the patient with Swyer-James-MacLeod syndrome. The perfusion study will show decreased activity in the affected lung with both Swyer-James-MacLeod syndrome and

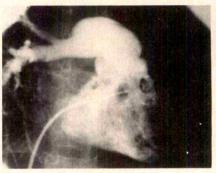


Figure 3.

congenital pulmonary artery hypoplasia, while there will be unilateral absence of pulmonary arterial blood flow in the patient with aplasia of a pulmonary artery.

Only rarely is any further diagnostic investigation required in an asymptomatic patient with suspected congenital absence of a pulmonary artery. However, in our patient, a cardiac angiogram (Fig 3) was obtained to evaluate the heart murmur. This study confirmed the diagnosis of the absence of the left pulmonary artery and documented a right aortic arch with mirror-image branching. A small atrial septal defect was also discovered.

An asymptomatic patient with a small hyperlucent lung may have unilateral absence of a pulmonary artery. The diagnosis can be made confidently with a ventilation-perfusion isotope lung scan.

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J. Wesley McWhorter, MPT, PhD (Contributor); Beverly P. Wood, MD (Section Editor)

A 21-month-old white female infant was examined in the pediatric clinic and referred to the physical therapy clinic with a diagnosis of torticollis. She was alert and afebrile, with normal vital signs and respiration. She presented with a cervical posture of forward and lateral flexion and rotation to the right. Further examination revealed point tenderness of the right sternocleidomastoid muscle. She was unwilling to undergo passive stretching of the right sternocleidomastoid muscle because of pain. Cervical spine roentgenograms were obtained to investigate possible anomalies or trauma (Figs 1 and 2).

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Therapy, The University of Texas Medical Branch
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Reprint requests to Department of Radiology, Childrens Hospital of Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90027 (Dr Wood).

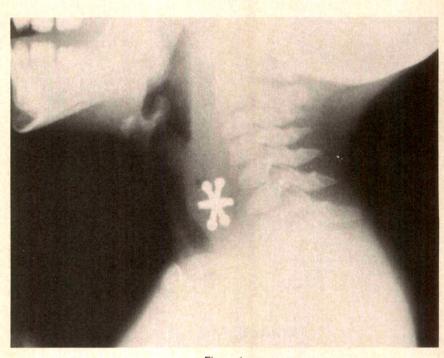
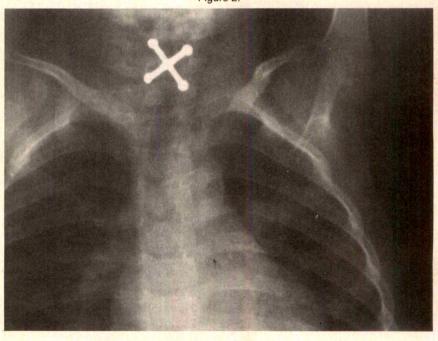


Figure 1. Figure 2.



Denouement and Discussion

Toy 'Jack' Aspiration Into the Hypopharynx

Fig 1.-Lateral roentgenographic view of cervical soft tissues showing a metal "jack" in the hypopharynx at the cricopharyngeal muscle. The trachea is displaced forward.

Fig 2.—Anteroposterior roentgenographic view of cervical spine showing foreign body.

Fig 3.—Example of the toy "jack," which was removed by direct endoscopy.

The patient was taken to the operating room, and while she was under general anesthesia a toy "jack" (Fig 3) was removed by direct endoscopy and rigid bronchoscopic forceps. It had been lodged in the hypopharynx. She tolerated the procedure well but developed a mild case of pneumonia subsequently.

More than 500 deaths due to asphyxiation following foreign body aspiration occur in the United States each year. Sixty percent of object aspirations occur in children aged less than 2 years.2 Male children are affected twice as often as female. Metal and plastic objects are less commonly aspirated, while edible objects (candy, nuts, grapes) are most frequently the cause of fatal cases.2,3

A foreign body in the hypopharynx may simulate one in the tracheal airway with extrinsic airway compression. Symptoms include choking, hoarseness, and stridor. Pain, drooling, and inability to swallow are seen with esophageal and hypopharyngeal foreign objects. With upper airway or high esophageal obstructing bodies, anteroposterior and lateral roentgenographic views of the cervical area are essential. The treatment of choice is

removal by forceps under direct visualization during endoscopy.1,2 Removal by Foley catheter is not recommended for objects with sharp projections; however, smooth objects in the esophagus may be removed in this manner.

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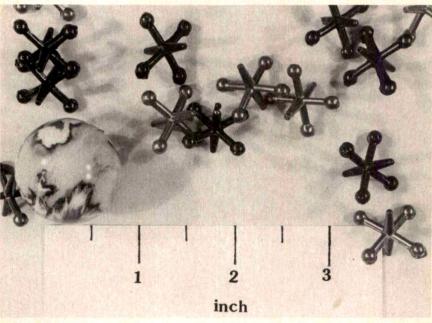


Figure 3.

Block Allergy Symptoms Before They Become Monumental

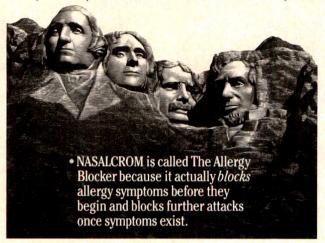
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Brief Summary

DESCRIPTION: Each milliliter of NASALCROM® Nasal Solution (cromolyn sodium nasal solution, USP) contains 40 mg cromolyn sodium in purified water with 0.01% benzalkonium chloride to preserve and 0.01% EDTA (edetate disodium) to stabilize the solution. **INDICATIONS:** NASALCROM is indicated for the prevention and treatment of the symptoms of allergic rhinitis.

CONTRAINDICATIONS: NASALCROM is contraindicated in those patients who have shown hypersensitivity to any of the ingredients.

PRECAUTIONS: General: Some patients may experience transient nasal stinging and/or sneezing immediately following instillation of NASALCROM. Except in rare occurrences, these experiences have not caused discontinuation of therapy.

In view of the biliary and renal routes of excretion for cromolyn sodium, consideration should be given to decreasing the dosage or discontinuing the administration of the drug in patients with impaired renal or hepatic function.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Long term studies in mice (12 months intraperitoneal treatment followed by 6 months observation), hamsters (12 months intraperitoneal treatment followed by 12 months observation), and rats (18 months subcutaneous treatment) showed no neoplastic effect of cromolyn sodium. No evidence of chromosomal damage or cytotoxicity was obtained in various mutagenesis studies.

No evidence of impaired fertility was shown in laboratory animal reproduction studies. **Pregnancy:** Pregnancy Category B. Reproduction studies with cromolyn sodium administered parenterally to pregnant mice, rats, and rabbits in doses up to 338 times the human clinical doses produced no evidence of fetal malformations. Adverse fetal effects (increased resorptions and decreased fetal weight) were noted only at the very high parenteral doses that produced maternal toxicity. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Drug Interaction During Pregnancy: Cromolyn sodium and isoproterenol were studied following subcutaneous injections in pregnant mice. Cromolyn sodium alone in doses of 60 to 540 mg/kg (38 to 338 times the human dose) did not cause significant increases in resorptions or major malformations. Isoproterenol alone at a dose of 2.7 mg/kg (90 times the human dose) increased both resorptions and malformations. The addition of cromolyn sodium (338 times the human dose) to isoproterenol (90 times the human dose) appears to have increased the incidence of both resorptions and malformations.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NASALCROM is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children below the age of 6 years have not

ADVERSE REACTIONS: The most frequent adverse reactions occurring in the 430 patients included in the clinical trials with NASALCROM were sneezing (1 in 10 patients), nasal stinging (1 in 20), nasal burning (1 in 25), and nasal irritation (1 in 40). Headaches and bad taste were reported in about 1 in 50 patients. Epistaxis, postnasal drip, and rash were reported in less than one percent of the patients. One patient in the clinical trials developed anaphylaxis

Adverse reactions which have occurred in the use of other cromolyn sodium formulations for inhalation include angioedema, joint pain and swelling, urticaria, cough, and wheezing. Other reactions reported rarely are serum sickness, periarteritic vasculitis, polymyositis, pericarditis, photodermatitis, exfoliative dermatitis, peripheral neuritis, and nephrosis.

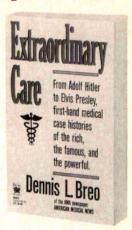
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Severe Respiratory Syncytial Virus Infection in Older Children

Jessie R. Groothuis, MD; Carol K. Salbenblatt, RN; Brian A. Lauer, MD

 Serious respiratory syncytial virus (RSV) disease requiring hospitalization occurs primarily in infants younger than 12 months. The incidence, risk factors, and clinical features in older children have not been studied extensively. Of 282 children hospitalized at our institution with severe RSV disease during a 3-year period, 62 (22%) were older than 12 months. These 62 older children were matched for sex, onset of illness, and hospital location with 62 hospitalized children vounger than 12 months with proved RSV infection. Older children had underlying chronic disease more commonly than younger children (47 of 62 vs 24 of 62). Chronic illnesses in older children included bronchopulmonary dysplasia and/or reactive airway disease (34 of 47), congenital heart disease (9 of 47), gastrointestinal disease (7 of 47), and genetic disorders (7 of 47). Three of the four deaths from RSV infection occurred in older children; all four had underlying disease (three with congenital heart disease and one with biliary atresia). We conclude that children older than 12 months with underlying disease are at increased risk for serious or fatal RSV infection and are not always protected by previous RSV disease. Such older children should be considered candidates for passive or active immunoprophylaxis against RSV infection as such agents become available.

(AJDC. 1990;144:346-348)

Respiratory syncytial virus (RSV) is the most important cause of lower respiratory tract infection in young children worldwide. 1-3 Disease severe enough to require hospitalization occurs primarily in infants younger than 12 months.⁴⁷ We reviewed the medical records of all children older than 12 months hospitalized with RSV disease during a 3-year period and compared their clinical features, outcome, and risk factors with matched children younger than 12 months. Our purpose was to determine whether a high-risk group of older children existed. Such children, prospectively identified, could be targeted for early immunization against RSV when vaccines or passive immunotherapy become available.

PATIENTS AND METHODS

Between 1985 and 1988, 282 children with RSV lower respiratory tract infection (pneumonia or bronchiolitis) were hospitalized in University Hospital, Denver, Colo. The RSV infection was confirmed by rapid RSV antigen tests (fluorescent antibody or enzyme immunoassay) and/or virus culture. The methods of specimen collection and RSV testing have been described previously.

Sixty-two (22%) of the 282 children were older than 12 months. For purposes of comparison, these 62 older children were matched in a case-control fashion for sex, date of illness onset, and hospital unit with 62 children younger than 12 months. This matching was done in an attempt to avoid differences in disease severity due to different viral strains or sex (males historically have more severe illness) and to equalize the number of patients requiring intensive care in each group. The charts of all 124 children were reviewed. Table 1 includes the epidemiologic data obtained. Table 2 describes the categories of chronic illness. The number of hospital days, whether RSV infection was acquired nosocomially (defined as RSV disease developing 4 or more days into a hospitalization for another illness), whether mechanical ventilation was required, and whether death occurred as a direct result of RSV illness were also noted.

Statistical analyses were performed using the paired Student t test for numeric variables and McNemar's χ^2 test for paired non-numeric variables.

RESULTS

Table 1 compares the epidemiologic and perinatal characteristics of the 124 study children (62 case-control pairs). No differences occurred between the two groups as to race and number of siblings and family members. The incidence of prematurity (defined as gestational age of less than 37 weeks) was higher in the older age group (P < .05). A greater number of older children required mechanical ventilation in the intensive care nursery (P < .05); however, no significant difference was found in the number of older or younger children who required oxygen supplementation. Fourteen (22%) of the older children had a documented history of RSV infection previously. Four (6%) of the children younger than 12 months had documented previous RSV infection.

Table 2 compares the underlying diagnoses in the two groups. Seventy-six percent (47/62) of older children were described as having underlying chronic disease as compared with 39% (24/62) of younger children (P < .001). In the older children, bronchopulmonary dysplasia and reactive airway disease (often found together) accounted for the largest group (34 of 47); congenital heart disease comprised the second largest category (9 of 47). Underlying gastrointestinal disease (7 of 47) and genetic disorders with pulmonary abnormalities (7 of 47) were also prevalent in older children (Tables 2 and 3). In contrast, nonorganic failure to thrive accounted for 6 of 24 cases of underlying disease in children younger than 12 months, as contrasted with only 3 of 47 children older than 12 months (P < .05). No differing characteristics were found between older and younger children without underlying disease.

Fourteen older children and 18 younger children required admission to the

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From the Department of Pediatrics, University of Colorado School of Medicine, Denver (Drs Groothuis and Salbenblatt); and Children's Health Care Center, Emanual Hospital and Medical Center, Portland, Ore (Dr Lauer).

Read before the 29th International Congress of Antimicrobial Agents and Chemotherapy, Houston, Tex, September 19, 1989.

Reprint requests to Department of Pediatrics, Box C-218, 4200 E Ninth Ave, Denver, CO 80262 (Dr Groothuis).

Table 1.—Demographic and
Perinatal Characteristics of
124 Study Children

	Age		
Characteristics	>1 y (n=62)	<1 y (n = 62)	
Demographic			
Age, mo (range) Race	23 (13-60)	4 (1-11)	
W	38	42	
В	8	8	
Other ·	16	12	
Family No.*	$4 \pm .21$	$4 \pm .18$	
Sibling No.*	$1.7 \pm .21$	$1.4 \pm .18$	
Perinatal			
Gestational age,			
wk*	$35 \pm 0.7 \dagger$	37 ± 0.5	
Birth weight, g*	2.3 ± 0.14	2.6 ± 0.12	
Ventilation			
required	23‡	11	
Oxygen			
required	29	23	

*Values represent mean ± SE. †P<.05 by paired Student's t test.

Table 2.- Underlying Disease in 124 Study Children*

124 Study Official			
	Age		
Disease	>1 y (n=62)	<1 y (n=62)	
Chronic lung disease			
Bronchopulmonary dysplæsia Reactive airway	19†	9	
disease	15‡	1	
Cystic fibrosis	o ·	1	
Other	3	0	
Congenital heart			
disease	9	9	
Genetic disorders	7	1	
Gastrointestinal			
disorders	7	4	
Failure to thrive	З§	6	
Total chronic disease	47	24	

*Many children had several diagnoses. †F<.05 by McNemar's χ^2 test.

§F<.01 by McNemar's χ² test.

intensive care unit. Four older and 5 younger children required mechanical ventilation. The incidence of nosocomially acquired RSV infection was similar for both groups; 8 older children and 11 younger children acquired RSV infection while hospitalized for other problems.

Four deaths due to RSV illness occurred in the 3-year study period. All four children who died had underlying disease; three had congenital heart disease, and one had biliary atresia. In all

Genetic Disease	No. of Children	Clinical Manifestation
VACTERL*	2	Tracheoesophageal fistula aspiration
Down syndrome	3	Pulmonary hypertension
San Luis Valley syndrome	1	Single-ventricle pulmonary hypertension
Verdi syndrome	1	Tracheostomy

*VACTERL indicates vertebral, anal, cardiac, tracheal, esophageal, renal, and fimb, designating a pattern of congenital anomalies.

deaths, deterioration from severe RSV disease was the final event. Two of the children (one 7 years old) who died had recently undergone cardiac surgery. Three of these deaths occurred in older children.

COMMENT

Severe RSV lower respiratory tract disease has been described predominantly in young infants.47 Glezen and coworkers4 found that 95% of children hospitalized with serious RSV disease were younger than 1 year; Parrott and coworkers demonstrated similar findings during a 1-year period. Our experience with RSV infection in older children with chronic lung disease led us to examine the incidence, risk factors, clinical characteristics, and outcome in the older children who develop serious RSV disease.

In contrast to other studies, we found that 22% (62/282) of all children admitted to our institution for severe RSV disease were older than 12 months. This may be in part a reflection of our tertiary care population; in any event, older children represented a significant proportion of those with RSV illness severe enough to require hospitalization.

An important finding in this study was that 76% (47/62) of these older children had underlying disease. Much of this was of pulmonary or cardiac origin. Other investigators have noted the susceptibility of young infants with cardiopulmonary disease to severe RSV illness.9-12 Older children with gastrointestinal and genetic disorders acounted for a second important and previously unrecognized group at risk for serious RSV disease. Many but not all of these children had severe pulmonary impairment associated with their underlying genetic disorder.

Almost one quarter (14 of 62) of the older children hospitalized had a previously documented history of RSV infection; they, nevertheless, again developed severe illness on reinfection. Because we used only laboratory-documented previous infection, this number may actually be a low representation of the previous RSV disease. It has been generally accepted that RSV reinfection is associated with milder disease.18,14 Several investigators, however, have found that RSV reinfection may be severe, particularly in those children who acquire their first RSV infection when younger than 6 months, when serologic responses may be poor, and in children with underlying cardiopulmonary disease. 9,15,16

Thirty-nine percent (24/62) of the children younger than 12 months hospitalized for serious RSV infection had chronic disease. Nonorganic failure to thrive was the underlying diagnosis in one third of these children. Failure to thrive has not been reported previously as a risk factor for severe RSV illness in the United States; however, a relationship between malnutrition and increased morbidity from acute respiratory infection has been described in young infants from studies done in developing countries. 17,18

The overall mortality was low (4/124 [3%]); however, three of the four deaths occurred in older children who had severe congenital heart disease. The overall mortality in this group (3/9 [33%]) was the same as that described by McDonald and coworkers10 and targets the cardiac population of all ages as that at greatest risk of death from RSV disease.

CONCLUSION

There is a group of children older than 12 months who are at risk for se-

[‡]P<.05 by McNemar's x2 test.

 $[\]sharp F < .001$ by McNemar's χ^2 test.

vere RSV disease. This group includes children with underlying pulmonary or cardiac disease and those with chronic gastrointestinal or genetic disorders, especially those with pulmonary involvement. Parents of older children at risk should be informed of the dangers of RSV illness, advised on how to minimize the risk of the child's developing RSV disease, and encouraged to seek early diagnosis of RSV infection. 9,19-21 Physicians caring for older high-risk children should consider early treatment with ribavirin for those with proved RSV infection. 22-24 High-risk children older than 12 months may be candidates for passive or active immunization against RSV infection when such immunoprophylaxis becomes available.

This work was supported in part by grant BRSG-05357 awarded by the Biomedical Research Support Grant Program, Division of Research Resources, National Institutes of Health and by National Institutes of Health contract NO1-A1-82520, Bethesda, Md.

Gary Zerbe, PhD, and Gulermo Marshall, PhD, provided statistical assistance; Mary Roth prepared the manuscript.

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Detection of Interleukin 1 β but Not Tumor Necrosis Factor– α in Cerebrospinal Fluid of Children With Aseptic Meningitis

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 Tumor necrosis factor α and interleukin 1B have been shown to be mediators of meningeal inflammation in animal models of bacterial meningitis. The presence of both cytokines in cerebrospinal fluid (CSF) of patients with bacterial meningitis has been documented recently. In this study, we measured concentrations of interleukin 16 and tumor necrosis factor-\alpha in CSF samples from 36 patients with nonbacterial (aseptic) meningitis, 13 of whom had culture-proved enteroviral meningitis, and from 14 control patients. None of the samples from patients with aseptic meningitis and from the controls had detectable tumor necrosis factor activity in CSF. Thirty-two (89%) of 36 patients with aseptic meningitis had detectable interleukin 1β in CSF (mean ± SEM. 48 ± 11 pg/mL). These concentrations were significantly smaller than those previously reported in patients with bacterial meningitis (944 \pm 128 pg/mL). Only 2 of the 14 control patients had detectable CSF interleukin 18 concentrations of 21 and 42 pg/mL. A significant correlation was evident between interleukin-1ß concentrations and white blood cell counts in the CSF of patients with aseptic meningitis. Our data suggest that the Initial events of CSF Inflammation in children with aseptic meningitis are different than those in patients with bacterial meningitis, and the participation of these two cytokines, especially tumor necrosis factor-a, is less critical to the process.

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Tumor necrosis factor— α (TNF α) and interleukin 1 β (IL-1 β), two macrophage-derived cytokines, play a major role in mediating tissue injury associated with gram-negative bacterial sepsis or endotoxemia. ¹⁵ Several investigators have demonstrated production of these two cytokines within the central nervous systems of animals with experimental meningitis and suggested their participation in the meningeal inflammatory cascade. ⁵⁸

The presence of both IL-1B and TNFα in the cerebrospinal fluid (CSF) of patients with bacterial meningitis has been documented recently. 6,0,10 Gramnegative enteric bacilli, group B strep-Neisseria meningitidis, Streptococcus pneumoniae, and Haemophilus influenzae type b induced production of TNF α and IL-1 β in CSF, and their concentrations were similar regardless of etiology. These data, derived from both animal models and clinical studies, suggest that IL-1B and $TNF\alpha$ contribute to the sequence of events that lead to meningeal inflammation. The complex interactions between the bacteria, these cytokines, and other substances (eg., arachidonic acid metabolites) is yet to be elucidated, but both TNF α and IL-1 β appear to be implicated in a common pathophysiologic pathway shared by gram-positive and gram-negative bacteria.

Viruses are responsible for many of the acute infections of the central nervous system, especially in the pediatric population. Young infants with acute nonbacterial meningitis can appear toxic and be difficult to distinguish, based on clinical grounds and CSF findings, from bacterial meningitis. Measurement of concentrations of TNF α and IL-1 β in the CSF of infants and children with aseptic meningitis might provide insight into the mechanisms of pathogenesis of virus-induced meningeal in-

flammation and provide a means by which to distinguish bacterial from nonbacterial infections in the subarachnoid space.

PATIENTS AND METHODS Study Groups

Thirty-six infants and children, between the ages of 1 month and 14 years, admitted from July to December 1988 to Children's Medical Center and Parkland Memorial Hospital, Dallas, Tex, with a diagnosis of aseptic meningitis, were evaluated prospectively. The following criteria were required to be enrolled in the study: (1) CSF leukocyte count of more than $10 \times 10^6/L$; (2) negative bacteriologic studies, including CSF and blood cultures, CSF gram-stained smear, and conventional antigen detection tests; and (3) no antibiotic therapy in the previous 2 weeks.

The CSF specimens were routinely cultured for bacteria and analyzed for white blood cell (WBC) count and differential cell count and for glucose and protein concentrations. Viral cultures were performed on all samples; 0.2- to 0.3-mL CSF aliquots were inoculated directly into human embryonic lung, A549, and rhesus monkey kidney cell lines. Occasionally, Buffalo green monkey kidney and MRC-5 cells were also included. These cultures were observed for a minimum of 14 days. A positive result was reported when definite cytopathic effect was noted. Isolates producing typical enteroviral cytopathic effects were identified by neutralization using the intersecting virus antiserum pools supplied by the Centers for Disease Control, Atlanta, Ga. The remaining CSF was stored at -70°C until assayed for TNF α and IL-1B.

A second group of CSF samples, considered as controls, was obtained from patients who were not suspected of having central nervous system infection and whose attending physicians requested CSF examinations. Lumbar puncture was performed in 12 patients as part of a routine workup for sepsis, in 1 patient who had a febrile seizure, and in another who had a possible afebrile seizure. All these specimens had WBC counts of less than $5 \times 10^6 {\rm L}$, normal glucose and protein

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concentrations, and negative bacteriologic studies. These samples were also kept at -70° C until assayed for cytokines.

A third group of 106 patients with bacterial meningitis was also included in the analysis. Complete data from these patients with bacterial meningitis were reported previously.

Written informed consent was obtained from the parents or legal guardians of all study patients. The study protocol was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center at Dallas.

Cytokine Assays

The CSF samples were assayed for IL-1 β using an enzyme-linked immunosorbent assay (ELISA).11 The optical densities were read on a computerized automated ELISA reader. The lower limit of sensitivity of the assay was 20 pg/mL at the 95% confidence level. The CSF samples with concentrations larger than the range of the standard curve (20 to 1000 pg/mL) were diluted in the bovine serum albumin phosphate-buffered diluent supplied with the commercial kit and reassayed to determine the precise concentration of IL-1\u03c3. This was only necessary when samples from patients with bacterial meningitis were measured. A mouse monoclonal antibody to human IL-13 reduced the IL-13 standards containing 50 to 500 pg/mL to below the sensitivity of the assay. After several representative CSF specimens were mixed with an equal volume of the antibody, IL-1β could no longer be detected in the assay.

The TNFα activity was determined by modification of a previously described cytotoxic assay.12 Briefly, L929 cells (CCL 1, American Type Culture Collection, Rockville, Md) were maintained in Dulbecco's modified Eagle medium supplemented with 10% fetal bovine serum and 4% penicillin and streptomycin. Confluent cultures were rinsed with sterile phosphate-buffered saline, then briefly with 0.05% trypsin, resuspended in fresh medium, and added to 96well plates $(7 \times 10^4 \text{ cells per well})$. After 2 to 3 hours in culture, 50 µL of cycloheximide (0.3 mg/mL) and 15 µL of CSF sample were added to each well, and the plates were incubated overnight (in 5% carbon dioxide at 37°C). Following microscopic evaluation, the medium was decanted, and the wells were filled with 100 μ L of 0.5% crystal violet in 25% methanol for 5 minutes, washed thoroughly with normal saline, and dried. The dye was solubilized with 100 µL of 50% acetic acid. The degree of cytotoxicity was quantified spectrophotometrically (at 490 nm) using a computerized automated ELISA plate reader. Equivalent concentrations of recombinant human TNFa were determined for experimental samples by interpolation of the recombinant human TNFα standard curve run simultaneously (0.1 pg/mL to 1 μ g/mL). Using this assay, we could reliably detect as little as 10 pg/mL of human TNF α . The samples were assayed in quadruplicate, and an SD within 10% of the mean was observed. Eight samples from patients with bacterial meningitis with the highest TNF α concentrations were reassayed in the presence and absence of anti-TNF α monoclonal anti-bodies.

Both TNF α and IL-1 β are believed to be stable for long periods when stored at -70° C (Bruce Beutler, MD, unpublished data, October 1989, and data on file, Cistron Biotechnologies, Pynebrook, NJ).

Statistical Methods

Comparisons between data from patients with a septic meningitis who had negative viral cultures and those with proved enteroviral meningitis were performed with the Student t test for independent groups. The Mann-Whitney U test was used to compare data from patients with bacterial and a septic meningitis. Finally, the strength of the relationship between CSF IL-1 β concentrations and other indexes of meningeal inflammation was a seessed with Spearman's correlation coefficients.

All data are expressed as mean \pm SEM unless otherwise indicated.

RESULTS

Thirteen (37%) of 35 patients with nonbacterial meningitis evaluated had a positive viral culture in rhesus monkey kidney cells. All isolates were identified as enteroviruses, and nine were typed as follows: three of echovirus 9, two of echovirus 11, and one each of coxsackievirus B2, echovirus 4, echovirus 5, and echovirus 31.

Because no significant differences occurred in the CSF WBC count and glucose and protein concentrations for patients with and without a viral isolate, we considered them as one group for the analysis (Table 1).

TNFα Concentrations

None of the 36 samples from patients with aseptic meningitis and from the 14 controls had detectable TNF α activity. By contrast, 79 (75%) of 106 CSF specimens obtained at diagnosis from patients with bacterial meningitis had measurable TNF α (787 \pm 326 pg/mL).

IL-1β Concentrations

Thirty-two (89%) of 36 patients with aseptic meningitis had detectable IL-1 β concentrations; the range of values was from less than 20 pg/mL to 400 pg/mL. No significant differences were evident between patients with positive viral culture (73.8 \pm 30.0 pg/mL) and those without a viral isolate (33.8 \pm 4.4 pg/mL; P = .54) (Table 1).

Two of 14 controls had IL-1 β concentrations (42 pg/mL and 21 pg/mL) near the lower limit of sensitivity for the assay.

Correlations between CSF IL-1 β and other indexes of CSF inflammation in patients with aseptic meningitis were also investigated. There was a significant correlation between CSF IL-1 β level and CSF WBC count (Spearman's coefficient=0.48; P=.003). No significant correlations were found for IL-1 β level and protein (r=.28; P=.09) and glucose (r=-.009; P=1.0) concentrations in CSF.

We compared CSF IL-1 β concentrations from patients with nonbacterial and bacterial meningitis. For this purpose, values from 36 patients with aseptic meningitis and from 106 patients with bacterial meningitis previously re-

Table 1.—Cerebrospinal Fluid (CSF) Findings and Interleukin 1 β (IL-1 β) and Tumor Necrosis Factor— α (TNF α) in Patients With Nonbacterial Meningitis*

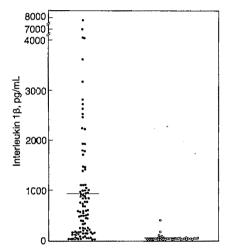
	Viral (
CSF Findings	Positive (n = 13)	Negative (n = 23)	P
WBC, ×10%/L	288±92	289 ± 85	.994
Glucose, mmol/L.	3.1 ± 0.2	2.9 ± 0.1	.63
Protein, g/L	0.19 ± 0.05	0.24 ± 0.04	.71
IL-1β, pg/mL	73.8 ± 30	33.8 ± 4.4	.54
TNFa†	ND	ND	

^{*}Values are mean ± SEM.

[†]ND indicates that levels were less than 10 pg/mL and were therefore considered not detectable.

ported* were analyzed. The difference between IL-1 β concentrations in these two groups of patients, 944 ± 128 pg/mL in patients with bacterial meningitis vs 48 ± 11 pg/mL in patients with aseptic meningitis, was highly significant (P<.0000001) (Figure).

Because these two patient groups had very different CSF WBC counts $(5233 \pm 1058 \times 10^6/L)$ and $288 \pm 62 \times 10^6/L$



Interleukin 1 β concentrations in the cerebrospinal fluid of infants and children with bacterial (solid circles) and nonbacterial (aseptic [P<.0000001] [open circles]) meningitis at diagnosis.

in patients with bacterial and aseptic meningitis, respectively) and because a strong correlation exists between the number of WBCs and IL-1 β concentrations in the CSF,* we evaluated IL-1 β concentrations in those patients of the two groups who had CSF WBC counts of 500×10^6 /L or less (Table 2). Although the CSF WBC counts were comparable for the two groups, the CSF IL-1 β concentrations were significantly greater (1180 \pm 61 pg/mL vs 48 \pm 11 pg/mL; P=.003) in patients with bacterial infection.

We assessed the potential role of measuring CSF concentrations of these two cytokines for diagnostic purposes to distinguish bacterial from nonbacterial meningitis (Table 3). For this analysis we included two groups: 106 patients with bacterial meningitis and 36 with aseptic meningitis. When a cut-off point of 100 pg/mL or greater of IL-16 in CSF was used, the sensitivity was 84.3%, the specificity was 94.4%, and the positive predictive value was 97.7%. With a cutoff of 10 pg/mL or greater of TNFα in CSF, the sensitivity was 74.5%, and the specificity and positive predictive values were 100%. Twenty-seven patients with bacterial meningitis had undetectable TNF α activity: of those patients. 18 had IL-1β concentrations of greater

than 100 pg/mL and would have been identified using this assay.

COMMENT

In recent years, the role of IL-18 and TNFα in the pathogenesis of meningeal inflammation has been investigated intensively. Studies in different animal models have provided evidence of their local production within the central nervous system. The TNFα activity has been documented in the CSF of mice injected intracerebrally with Listeria monocytogenes6 and in the CSF of rabbits inoculated intracisternally with H influenzae type b or its purified lipooligosaccharide.8 Likewise IL-1 has been detected in the CSF of rats after intracisternal inoculation of lipo-oligosaccharide.7 Findings derived from experiments using specific polyclonal or monoclonal antibodies directed against these cytokines and from the application of purified recombinant materials that can reproduce their actions in the animal models confirmed their role in the complex sequence of events involved in meningeal inflammation.8,13

These two cytokines have been demonstrated in the CSF of patients with bacterial meningitis. 6,8,10 Leist et al6 detected TNFa in the CSF of three of seven patients with bacterial meningitis. We documented TNF a activity in 79 (74%) of 106 CSF specimens obtained at diagnosis from infants and children with meningitis caused by H influenzae, S pneumoniae. N meningitidis. and group B streptococcus,9 and from 25 (92%) of 27 neonates with gram-negative enteric bacillary meningitis. 10 By contrast, none of 36 patients with aseptic meningitis evaluated in the present study had detectable TNF a activity.

The lack of TNF α activity in the CSF of patients with aseptic meningitis is consistent with observations by others. 6,14 These studies used the cytolytic assay and an ELISA system, and both failed to demonstrate CSF TNF a activity. This is further supported by experiments in which intracerebral inoculation of mice with lymphocytic choriomeningitis virus failed to elicit TNFα activity. 6 On the other hand, previous in vitro investigations showed that certain viruses induced production of TNFa from blood mononuclear cells. 15,16 Several circumstances may

Table 2.—Cerebrospinal Fluid (CSF) Interleukin 1 β (IL-1 β) Concentrations in Patients With Meningitis With CSF White Blood Cell (WBC) Counts of Less Than 500×10 $^{\circ}$ /L*

	Type of		
	Bacterial (n = 12)	Nonbacterial (n = 36)	P
WBC, ×10%L	295 ± 43	288 ± 62	.199
IL-1β, pg/mL	1180±61	48±11	.003

^{*}Values are mean ± SEM.

Table S.—Diagnostic Value of Cerebrospinal Fluid (CSF) Interleukin 1 β (IL-1 β) and Tumor Necrosis Factor— α (TNF α) Concentrations to Distinguish Bacterial From Nonbacterial Meningitis

	IL-1β in CSF		TNFα in CSF	
•	≥100 pg/mL	<100 pg/mL	, ≥10 pg/mL	<10 pg/mL
Patients with meningitis Bacterial, No.	86	16	79	27
Nonbacterial, No.	2	34	0	36
Sensitivity, %	84.3 (8	36/102)	74.5 (7	79/106)
Specificity, %	94.4 (3	34/36)	100 (3	36/36)
Predictive value, %	97.7 (8	36/88)	100 (7	79/79)

contribute to this apparent discrepancy. First, the viruses used in the latter in vitro experiments differed from those commonly isolated from patients with aseptic meningitis. Second, the cells that are the probable source of $TNF\alpha$ in the central nervous system, astroglia and microglia, ^{17,18} might respond to viruses differently than do blood mononuclear cells. Additionally, it is possible that $TNF\alpha$ is induced by enteroviruses, but in amounts that are below the detectable limit of the assay system.

The IL-13 was detected in 32 (89%) of 36 patients with aseptic meningitis. Previously, we found this cytokine in 97 (95%) of 102 infants and children with bacterial meningitis. Although the percentage of patients whose CSF samples contained measurable amounts of IL-1B did not substantially differ, the concentrations detected in patients with bacterial meningitis were, on average, 20fold greater than those in patients with aseptic meningitis (Figure). This was also true when only the patients with bacterial meningitis who had WBC counts of less than 500×106/L in CSF were compared with those with aseptic meningitis (Table 2). There was a significant correlation between IL-18 concentrations and WBCs in CSF (Spearman's coefficient = .48; P = .003) despite the relatively small number of patients with aseptic meningitis evaluated. This is consistent with our previous findings in bacterial meningitis where CSF IL-1B concentrations correlated significantly with the concentrations of WBCs, protein, lactate, and glucose in CSF.5

The larger concentrations of IL-1B in the CSF of children with bacterial meningitis were anticipated. Bacterial components, such as lipopolysaccharide19 and teichoic acid, are potent stimuli of IL-1 production. By contrast, scant information exists regarding viral induction of IL-1. Helminen and Vesikari²⁰ found that systemic bacterial infections produced spontaneous release of IL-1 from peripheral blood monocytes, whereas uncomplicated viral infections usually did not. In addition, several viruses have been shown to have an inhibitory effect on IL-1 activity. Cytomegalovirus decreased IL-1ß production from peripheral blood monocytes.21 Infection of human thymic epithelial cells by cytomegalovirus,

coxsackievirus B1, and respiratory syncytial virus resulted in a marked reduction of measurable IL-1 activity.²² This occurred in the absence of any detectable cytopathic effect.

The almost complete absence of TNFα and IL-1β in normal CSF samples obtained from the control group provides support for their participation in the inflammatory response. Two control patients had IL-1β concentrations in CSF that were at the lower limit of sensitivity for the assay. Our data suggest that the initial events of CSF inflammation in children with aseptic meningitis are different from those in patients with bacterial meningitis, and that the participation of these two cytokines, especially of $TNF\alpha$, is less critical to the process. Further investigations in this respect are needed.

The significant differences in CSF concentrations of IL-1β and TNFα for these two groups of patients might be used for diagnostic purposes to distinguish bacterial from nonbacterial meningitis (Table 3). However, the assays used, although very sensitive, were cumbersome and involved overnight incubation. Development of faster and more easily performed assays is required, and a larger group of patients with nonbacterial meningitis should be studied before determination of CSF IL-1 β and TNF α concentrations can be considered a practical screening test to distinguish patients with bacterial meningitis from those with nonbacterial meningitis.

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Tumor Necrosis Factor α and Interleukin 1 β in Synovial Fluid of Infants and Children With Suppurative Arthritis

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• Tumor necrosis factor α and interleukin 16 concentrations were measured in synovial fluid of 24 infants and children with diagnoses of suppurative arthritis (n=16) and other kinds of arthritis (n=8). Large concentrations of tumor necrosis factor α (range, 100 to 85 000 pg/mL) were found in 12 (75%) of 16 patients with bacterial infection and in none of the patients with noninfectious origins. Large concentrations of interleukin 1ß (>200 pg/mL) were found in 15 (94%) of 16 patients with bacterial infection and in none of the other patients. In the latter group, small concentrations of interleukin 1 (range, 40 to 120 pg/mL) were present in 5 (63%) of 8 patients. Serum samples obtained simultaneously were negative for both cytokines. Tumor necrosis factor α and interleukin 18 concentrations correlated significantly and with leukocyte counts in synovial fluid. We conclude that large concentrations of tumor necrosis factor α and interleukin 16 are produced locally in patients with suppurative arthritis and they may be potentially useful in differentiating this condition from other kinds of arthritis.

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I nterleukin 1 (IL-1) and tumor necrosis factor (TNF) have been implicated as key mediators of host responses to microbial invasion and immunological insults, and they play a major role in inflammatory processes. ¹³ Initially described as a product of activated macrophages, TNF and especially IL-1 are now known to be produced by a great variety of cells, including synovial fibroblasts. ⁴⁵ Once released, they can trigger the infiltration of polymorphonuclear leukocytes (PMNs) into numerous tis-

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sues with consequent induction of secondary mediators in local areas. ⁶⁸ It has been suggested that these cytokines are important in the inflammatory reactions that occur in rheumatoid arthritis, since they elicit collagenase secretion, prostaglandin E₂ synthesis, and intracellular proteinase release by human synovial cells. ^{5,10} Also, it is known that several bacterial antigens, such as lipopolysaccharide and peptidoglycan fragments, are powerful stimuli for the production of both cytokines by macrophages and monocytes. ^{5,6,11}

In view of these considerations, we decided to investigate the presence of both cytokines in synovial fluid of children with suppurative or noninfectious arthritides and to define any possible correlation between them and synovial inflammatory indexes.

PATIENTS AND METHODS Patients

Twenty-four infants and children, aged 2 months to 15 years, admitted to Children's Medical Center or Parkland Memorial hospital in Dallas, Tex, with diagnoses of any kind of arthritis requiring diagnostic aspiration of synovial fluid were enrolled from July 1988 through May 1989. Clinical and laboratory findings of these patients were recorded. No informed consent was obtained, since this study was qualified for exempted research by the institutional review board.

Collection of Samples

Synovial fluid was collected from joint arthrocentesis performed for diagnostic purposes by orthopedic surgeons. A blood sample was obtained simultaneously in these patients. Samples were centrifuged at 1500g for 10 minutes to remove cells and then stored at $-70^{\circ}\mathrm{C}$ until assayed. The rest of the sample was sent to the laboratory for routine cytologic, bacteriologic, and biochemical analyses.

Assays for Cytokines

Tumor necrosis factor a activity was determined by modification of a previously described cytotoxic assay using L929 cells. 12 The degree of cytotoxicity was quantified spectrophotometrically (490 nm) using a computerized automated microplate reader (Biorad Model 2550 EIA Reader, Hercules, Calif). Recombinant human TNFa in concentrations of 1 pg/mL to 1 mg/L were tested simultaneously to make a standard curve. The lower limit of sensitivity for this assay was 10 pg/mL. To test that the L929 cytotoxicity of the synovial fluid was mediated by $TNF\alpha$, positive samples were assayed again in the presence of monoclonal antibody specific for human TNFa and complete elimination of cytotoxicity was observed. Tumor necrosis factor is stable for long periods when stored at -70°C (B.B., unpublished data,

Interleukin 1 β activity was determined using an enzyme-linked immunosorbent assay (ELISA) commercially available (Cistron Biotechnologies, Pynebrook, NJ). The lower limit of sensitivity of the assay was 20 pg/mL at the 95% CI. Samples with IL-1 β concentrations larger than the range of the standard curve (20 to 1000 pg/mL) were diluted in bovine serum albumin phosphate buffer and assayed again to determine the precise concentration.

Statistical Analyses

Comparison of means between independent groups was performed using the two-tailed t test. Two-tailed Fisher's Exact Test was used to compare proportions between groups. Spearman's correlation coefficients between TNF and IL-1 concentrations and those of other synovial inflammatory indexes were calculated to investigate the strength of relationship between pairs. The level of significance was set at $P \le .05$.

RESULTS

Twenty-four infants and children were enrolled and evaluated. Of those, 16 patients were classified as having

Table 1.—General Characteristics of Patients With Suppurative Arthritis and With Noninfectious Synovial Effusions*

Characteristic	Suppurative Arthritis (n = 16)	Noninfectious Arthritides (n=8)
Median age, mo (range)	15 (2 mo-15 y)	19 (9 mo-14 y)
Male	11 (68)	3 (38)
Duration of symptoms before arthrocentesis, mean ± SEM, d	4.4 ± 0.6	3.7±0.5
Single joint involved	16 (100)	6 (75)
Fever (>38°C)	13 (81)	5 (63)
ESR (>50 mm/h)	10 (62)	3 (38)
WBC (>10×10°/L)	10 (62)	5 (63)

^{*}Data are expressed as the number (percent) of patients unless indicated otherwise. No significant differences were observed between both groups of patients by Fisher's Exact Test and Student's t test. ESR indicates erythrocyte sedimentation rate; WBC, white blood cell count.

Table 2.—Synovial Fluid Analysis of Patients With Suppurative Arthritis and With Noninfectious Arthritides*

Characteristic	Suppurative Arthritis (n = 16)	Noninfectious Arthritides (n=8)	P†
Leukocytes, ×10°/L	92.2 ± 13.1	33.1 ± 12.2	<.05
Polymorphonuclear leukocytes, ×10°/L	83.9 ± 2.8	25.1 ± 5.6	<.01
Glucose, mmol/L	1.8 ± 0.4	2.6 ± 0.3	NS
Protein, g/L	33.9 ± 1.9	22.8±6.3	NS
TNF (>10 pg/mL)	12 (75)	0	<.001
IL-1 (>200 pg/mL)	15 (94)	0	<.0001

^{*}Data are expressed as the mean ± SEM or the number (percent) of patients. TNF indicates tumor necrosis factor; IL-1, interleukin 1.

 $[\]dagger$ Significance was measured by Fisher's Exact Test and Student's t test. NS indicates not significant.

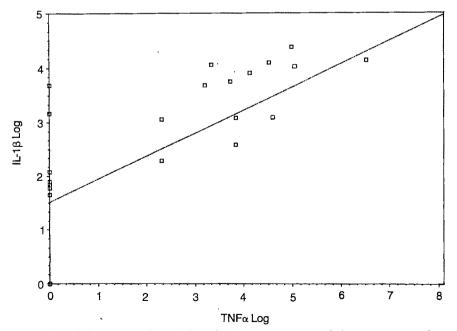


Fig 1.—Correlation between interleukin 1 β (IL-1 β) and tumor necrosis factor α concentrations (TNF α) in synovial fluid of 24 children with infectious and noninfectious arthritides. Four patients had neither TNF α nor IL-1 β detected. Spearman's r= .819; P= .000003.

suppurative arthritis and 8 as having other kinds of arthritis. The clinical and laboratory characteristics of these patients are summarized in Table 1.

In patients with bacterial infection, Haemophilus influenzae type b was recovered from synovial fluid in five patients. Staphulococcus aureus in four. Streptococcus pneumoniae in two, Streptococcus pyogenes in one, Salmonella group B in one, and Kingella kingae in one. In two patients, no organism was isolated from joint fluid: one had concomitant osteomyelitis caused by S aureus, and in the other, the diagnosis was based on clinical grounds, high erythrocyte sedimentation rate (120 mm/h), significant changes in synovial inflammatory indexes (white blood cell count, 135×109/L; glucose level, 0.56 mmol/L; and protein level, 0.04 g/L), and rapid response to antimicrobial treatment. Two patients had received previous oral antimicrobial therapy but organisms were recovered from joint fluid in both cases. Blood cultures were positive for H influenzae type b in two patients.

In the group of patients with noninfectious arthritides, three were considered to have traumatic effusions; three, reactive arthritis; and two, juvenile rheumatoid arthritis. The diagnosis of reactive arthritis was based on the presence of one or more characteristics, such as multiple joint involvement, previous episode of diarrheal illness, positive HLA-B27 marker, and failure to isolate microorganisms from blood, bone, or synovial fluid.

The synovial fluid analysis results of all patients are shown in Table 2. There were significant differences between both groups regarding leukocyte and PMN cell counts and cytokine concentrations.

Tumor necrosis factor α was not detected in the group of patients with noninfectious arthritides. In contrast, three quarters of patients with suppurative arthritis had detectable TNF α in synovial fluid with a mean \pm SEM of $18\,628\pm7762\,$ pg/mL (range, 200 to $85\,000\,$ pg/mL). Tumor necrosis factor α was detected in all seven patients with suppurative arthritis caused by gramnegative organisms (39 $000\pm15\,934\,$ pg/mL), whereas it was found in four of seven patients with gram-positive orseven

ganisms (2300 \pm 1371 pg/mL) (P = .07). Tumor necrosis factor α was also present in one patient with presumed suppurative arthritis but sterile joint fluid (6500 pg/mL).

Interleukin 1β was detected in all but one patient with suppurative arthritis (mean \pm SEM, 8418 ± 2198 pg/mL; range, 400 to 26 000 pg/mL), and in five (63%) of eight patients with noninfectious origin (79 \pm 8.1 pg/mL; range, 45 to 120 pg/mL) (P<.01). In this latter group, IL-1 β was detected in all three patients with juvenile rheumatoid arthritis, in two of three with reactive arthritis, and in none of three patients with traumatic effusions.

In the patient with suppurative arthritis who did not have detectable IL-1 β , S aureus was recovered from synovial fluid and from bone aspirate. This patient did not have detectable TNF α either.

In a group of six patients with suppurative arthritis who had a leukocyte count less than $50\times10^{9}/\mathrm{L}$ in synovial fluid (mean \pm SEM, $38.2\times10^{9}/\mathrm{L}\pm8.6\times10^{9}/\mathrm{L}$) and comparable counts with those with noninfectious nontraumatic effusions $(42.6\times10^{9}/\mathrm{L}\pm12.2\times10^{9}/\mathrm{L})$, the mean IL-1 β concentrations were 27 times greater (2133 \pm 530 vs 79 \pm 8.1 pg/mL, respectively) (P<.05). The mean IL-1 β concentration in those patients with gram-negative infection was $14\,071\pm3314$ pg/mL compared with 4556 ± 2658 pg/mL in those with gram-positive infection (P>.10).

Tumor necrosis factor α and IL-1 β concentrations correlated significantly (P<.0001) and each correlated with leukocyte counts in synovial fluid (P=.026 and P<.0001, respectively) (Figs 1 through 3). There was no correlation between cytokines and other inflammatory indexes.

Serum samples obtained simultaneously were negative for both cytokines.

COMMENT

Suppurative arthritis is defined as an inflammatory reaction within the joint space following synovial infection caused by a variety of organisms. It is usually manifested by fever and symptoms related to the joint involved, such as pain, limitation of motion, swelling, and presence of effusion. These patients

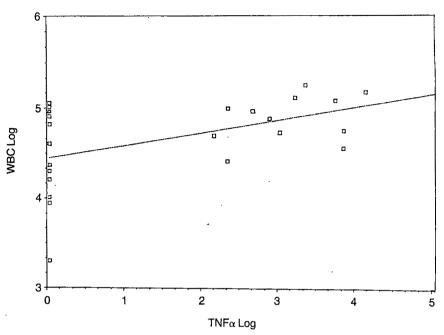


Fig 2.—Correlation between white blood cell counts (WBC) and tumor necrosis factor α (TNF α) concentration in synovial fluid of 24 children with infectious and noninfectious arthritides. Spearman's r=.555; P=.026.

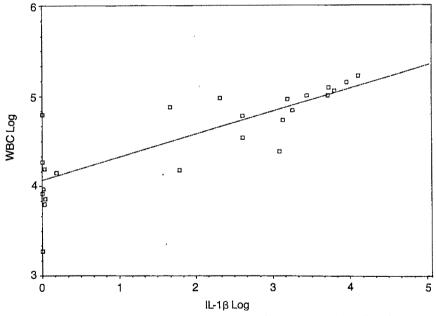


Fig 3.—Correlation between white blood cell counts (WBC) and interleukin-1 β (IL-1 β) concentration in synovial fluid of 24 children with infectious and noninfectious arthritides. Spearman's r=.902; P=.00002.

frequently have an elevated erythrocyte sedimentation rate and white blood cell count with a predominance of PMNs. Analysis of joint fluid shows, in many cases, a leukocyte count greater than 100×10^9 /L, with a differential count of more than 90% PMNs, glucose

level less than 2.2 mmol/L, and elevated protein concentration. However, all these clinical and laboratory findings are not specific for bacterial arthritis, since some other inflammatory conditions, such as rheumatoid arthritis, rheumatic fever, and reactive arthritis,

can be at times indistinguishable from cases of suppurative arthritis. 18,14 In this study, only the leukocyte counts and especially the PMN counts were significantly different between patients with suppurative and noninfectious arthritis, but there was overlap in values.

Regarding pathogenesis of these conditions, it has been known for many years that bacterial products and immune complexes can provoke the infiltration of leukocytes into synovial spaces, and they in turn can produce tissue damage by releasing harmful substances locally. Recent investigations have stressed the importance of two cytokines, TNF and IL-1, as the key mediators in the inflammatory cascade that occurs after microbial invasion and immunologic insults.1,15 The production of TNF and IL-1 can be strongly elicited by exposure of sensitive cells to endotoxin (lipopolysaccharide) of gram-negative bacteria. 6,11 but other stimuli, such as cell-wall fragments of gram-positive bacteria, immune complexes, and other substances, can induce their release. 5,16

Tumor necrosis factor and especially IL-1 have been found in synovial fluid of patients with various kinds of arthritis, and it is believed that they are produced by resident synovial cells after stimulation with bacterial or immune products. 17-19 Once produced, they can trigger the emigration of leukocytes into the synovial space, with the subsequent activation of arachidonic acid metabolism, release of collagenases and proteolytic enzymes, and other destructive substances that might contribute to joint damage. 7,9 In addition, incoming monocytes and PMNs can produce IL-1. thus amplifying these host responses. 20,21 On the basis of our findings, it seems that gram-negative bacteria products are very powerful stimuli for TNF α and IL-1 β production, since in all patients infected with these organisms larger amounts of these cytokines were found in synovial fluid than in patients infected with gram-positive bacteria in whom smaller concentrations of TNF and IL-1 were detected (60% and 86%, respectively). Tumor necrosis factor a was not detected in any patient with noninfectious arthritis, whereas IL-1β was present, although in very small concentrations, in more than half of these

patients. In this regard, several investigators have demonstrated the presence of small amounts of TNF and IL-1 in synovial fluid of adults with rheumatoid arthritis and other forms of immunologically mediated arthritis. 17,18,22 Moreover, presence of IL-1 α and IL-1 β messenger RNAs and of TNF α and TNF β messenger RNAs have been detected in patients with rheumatoid arthritis.28 In our study, presence of TNFa but no TNFB activity was confirmed by neutralization of cytotoxicity after reincubating positive samples with antihuman TNF α monoclonal antibody. It is also important to take into account that other cytokines, such as interferon or IL-1, could amplify the toxicity of TNF, so the TNF bioassay data actually may represent a sort of composite toxicity resulting from exposure to several cytokines.24

It is unlikely that the difference in IL-18 concentration between patients in both groups could be only attributable to the greater number of incoming leukocytes in patients with bacterial arthritis, since in patients with comparable leukocyte counts the IL-1 concentration was significantly higher in those with bacterial infection.

As our understanding of the role played by TNF and IL-1 in mediating the inflammatory response continues to grow, we might anticipate that means will be found to abolish selectively the detrimental effects caused by overproduction of these cytokines and to find new therapeutic interventions in addition to antimicrobial agents to diminish sequelae left after bacterial infections.

Finally, the high concentration of these cytokines in synovial fluid might offer a useful diagnostic marker to differentiate between bacterial infection and other kinds of inflammatory conditions, especially in selected cases when other indexes of synovial inflammation are not remarkably altered. Because of the limited number of patients with noninfectious arthritides in this study, further research is warranted to define precisely their applicability for diagnostic purposes.

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Children's Television-Viewing Habits and the Family Environment

Howard L. Taras, MD; James F. Sallis, PhD; Philip R. Nader, MD; Julie Nelson

· Pediatricians are encouraged to modify the impact of television on children, based on the assumption that parents mediate children's viewing habits through the home environment. Sixty-six parents of children aged 3 to 8 years responded to an interviewer-administered questionnaire. Responses to questions on family environment were compared with reported childhood viewing of educational programming (Public Broadcasting Service) and the child's television-viewing hours. Most homes surveyed had a videocassette recorder, cable television, and more than one television set. Frequent parental discussion of program content with children was reported by 38% of respondents. Availability of television and parent-child discussion of content were not correlated with viewing hours or viewing Public Broadcasting Service. Frequent use of television as a distraction for the child correlated positively with viewing hours. Viewing Public Broadcasting Service correlated negatively with parentchild coviewing and with use of television as a form of entertainment. Children's own television viewing content correlated positively with viewing Public Broadcasting Service. Of all measured factors in the home environment, parental attitudes were most closely associated with children's viewing habits.

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Pavorable and unfavorable effects of television (TV) viewing on children are still being studied and debated. Let Yet various organizations, including the American Academy of Pediatrics, have proposed that parental discussion of program content with children, coviewing with children, and supervision of content selection may encourage TV-viewing habits in children that will optimize TV's positive influence on youth. 59

There is evidence that, despite modest educational efforts, most parents do not regularly act as mediators in this way. Only 15% of parents guide their children to watch or not to watch certain TV programs. Most parents do not frequently discuss programs with their children, although they occasionally comment about TV in a casual manner. It may be worthwhile for pediatricians to encourage parents to modify their children's viewing habits through other means.

Parents may mediate their children's viewing habits in ways that are more subtle and effective than discussion, coviewing, and guidance to programming. Parents' attitudes to TV, how they use TV in the home, and the availability of TV may be the subtle ways by which they set an atmosphere within their family system that influences the quantity and quality of TV their child watches. Since no single aspect of family interaction can predict the influence of TV on the child, is it is important to expand our understanding of the familial influences on children's TV viewing.

Questions addressed in this study are as follows: (1) Is a child's TV-viewing time associated with the availability of TV to the child, parental attitude to the child's TV viewing, and parents' reported discussion and coviewing practices? (2) Is the viewing of educational programming by a child associated with these family environmental factors?

METHODS Subjects

The surveyed population was composed of 66 parents of children aged 3 to 5 years attending preschool (55%), and children aged 6 to 8 years attending elementary school

(45%). For parents with more than one child, only one child was selected by investigators for the parent to consider, with regard to the survey. The population was recruited from a public elementary school and an adjoining government-subsidized day-care center in a mixed Anglo/Hispanic working-class suburb of San Diego, Calif. Over 90% of all parents approached at the school's "health fair" were successfully recruited into the study. In the surveyed population, 48% of families had at least one parent with more than a high school education, 12% were single-family households, 63% described themselves as Hispanic, and 30% preferred the Spanish language for the interview. There were no significant demographic differences between families of the preschoolers and those of the elementary school children.

Questionnaire

An interviewer-administered survey in Spanish or English was used to elicit a total of 30 multiple-choice and one-word responses. The questionnaire was given on two occasions to investigate reliability, and was compared with previously published norms to investigate validity. ¹³ Interviews were conducted either at home or at school, 2 to 3 weeks apart. The child's viewing habits surveyed here included the number of hours TV was viewed per week and whether the Public Broadcasting Service (PBS) was viewed. Parents were asked to base their responses on events occurring in the preceding 6-month period.

Data Analysis

Frequency distribution of responses, Pearson coefficients, and χ^2 analyses were performed using the Statistical Package for the Social Sciences (SPSS-X).¹⁴

RESULTS TV-Viewing Habits

Children watched an average of 21.4 hours of TV per week, and 76% regularly watched PBS. The day-care population watched 25 hours of TV per week. This was significantly more hours than

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the 17 hours per week for school-aged children (P=.02). Sixty-six percent of children in Hispanic families watched PBS, compared with 95% of children of other ethnic groups (P=.04). Other demographic variables, such as education and number of adults per household, were not significantly associated with reported viewing of PBS or viewing hours.

Availability

At least one TV was available in every home. The percentage of homes with cable TV, more than 1 TV set, a videocassette recorder (VCR), and a TV in the child's own bedroom are listed in Table 1. Age of the child was not associated with the availability of TV. Thirty-two percent of Hispanic families had a TV in the child's bedroom. This is significantly more than the 14% of other ethnic groups (P = .05). Among families where at least one parent had more than a high school education, 83% had a VCR. This compares with 46% of families with less education (P = .004). Only 12% of single-parent families had a VCR, compared with 70% of families with more adults at home (P=.003). Twelve percent of single-parent homes had more than one TV set, compared with 92% of homes with more than one adult (P < .001).

Parental Attitudes and Reported Practices

Twenty percent of respondents stated that they watched TV with their child more than half of the viewing hours, and 38% frequently discussed the content of TV with their child. Parents were questioned on how TV viewing was used for their child at home. They could respond "often," "sometimes," or "rarely" to each use of TV. More mothers responded that TV was used "often" as a source of entertainment than for other purposes, as shown in Table 1. Given the choice of "strong," "moderate," or "weak," mothers reported their own "strong" influence on the content of their child's TV viewing more frequently than they reported a "strong" influence by other family members (Table 1). Demographic variables were not associated with responses to parental attitudes and practices.

Table 1.—Associations Between Family Environment and Children's TV-Viewing Habits*

	Response, %	Association With Viewing Time, P	Association With Watching PBS, P
Availability			
TV in child's bedroom	22	†	
VCR at home	62		
More than 1 TV	55		
Cable TV	63		
Parental involvement		•	
Programs discussed "frequently"	38		
Coviewing with child >50% time	20		<.004
Parents "often" use TV for child's			
Entertainment	66		<.002
Educational tool	44		<.02
"Safe distraction"	22	.01	
Reward	14		
Lead-in to discussion	12		***
"Strong" influence on child's program choice			
Mother	65		
Father	32		
Child	27	***	<.04
Sibling	20		• • •

^{*}TV denotes television; PBS, Public Broadcasting Service; and VCR, videocassette recorder. †Ellipses denote an association where P was not statistically significant.

Factors Associated With Viewing Hours

The use of TV as a distraction by parents was associated with the child's viewing time. When TV was used "often" as a safe distraction, an average of \$0 hours per week was reportedly watched. This was significantly more hours than when TV was used "sometimes" (20 h/wk) or "rarely" (17 h/wk) as a safe distraction (P=.01).

Other uses of TV for the child, availability, coviewing time, and the influences on content by various family members were not found to be associated with the quantity of children's TV viewing.

Factors Associated With Viewing PBS

Parents were more likely to respond that their children viewed PBS if they also responded as follows: that TV was not used as a form of entertainment; that it was used often as an educational tool; that they did not view TV with their child more than 50% of the time; and that their child had a strong influence on program selection (Table 2).

Availability of TV, its use as a safe

Table 2.—Family Environment
Association With Child's Viewing PBS*

	Watch PBS,	
	%	t Test
Parent response TV used as form of entertainment		
"Often"	79	n = 000
"Not often"	89	P<.002
TV used as educational tool "Often"	93	P<.02
"Not often"	64	F<.02
Coviewing with parent ≥50% time	53	P<.004
<50% time	80	F<.004
Child's influence on program selection Strong	89	:
Strong	69	P<.04
Not strong	71	
***** * * * * * * * * * * * * * * * *		

^{*}PBS denotes Public Broadcasting Service; TV, television.

distraction, reward, or lead-in to discussion, and the influences of parents and siblings on the child's programming content were not associated with whether PBS was viewed.

COMMENT

The results here are based on selfreported behaviors and are thus at risk for socially desirable response bias. However, the parents' responses indicated that this was not a major factor. For instance, more parents reported that TV was used for entertainment than it was for education or discussion. Only one set of respondents in five reported large amounts of coviewing with their child. Responses that could be described as socially desirable in one item of the questionnaire were not correlated with socially desirable responses on other items. Therefore, it does not appear that even a minority of subjects were responding consistently to what they "ought" to be doing at home with their children.

Viewing habits, such as hours per day viewed by the studied age groups, were consistent with the findings of previously published studies.15 A drop in viewing hours when children enter elementary school, prior to the subsequent increase in viewing hours, has also been previously described. 15 Most responses associated with demographic variables were in the expected directions. Fewer Hispanic children watched PBS, and this may be because of the local availability of commercial Spanish-language TV. Better-educated families and families with more than one adult may be more likely to afford a VCR and this would account for the higher availability of this item among the more well educated. It is more difficult to speculate why Hispanic children would be more likely to have TVs in their own bedrooms.

The quantity of TV viewed by children was not associated with the availability of TV or parental practices. Viewing was associated with how the parents reported using TV in the home. In pilot testing, few parents would endorse using TV as a "babysitter" so

the phrase "safe distraction" was substituted for a less socially undesirable connotation. Children of parents who used TV in this manner watched more TV than other children. It will be important to study additional parental attitudes toward TV and parents' own TV-viewing habits in more depth in future studies.

The quality of TV viewing was assessed here solely by whether PBS was watched regularly in the preceding 6month period. It is arguable that quality programming for children is available on commercial channels. However, as there are no commercial networks that air educational programs in the early mornings or after school for young children during the weekdays, and as PBS programming has been documented to have a strong educational component without commercial advertising, viewing PBS provides a limited but meaningful indication of quality programming. As parents (especially mothers) have a strong influence on the content of TV viewing by their children, it is not surprising that PBS is more likely to be viewed regularly by children whose parents do not often use TV as a source of entertainment, and by children of parents who use TV often as an educational tool.

It was surprising to find that PBS was watched more in homes where the child has a strong influence on his or her program content and where parents do not frequently watch TV with the child. These findings suggest that children prefer PBS over commercial networks, but when children and parents view TV together, they watch the commercial channels that the parents prefer. Therefore, coviewing, which is proposed as a practice to improve the TV

viewing experience for children, may paradoxically decrease the quality of TV content to which the child is exposed.

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Calcium Retention From Milk-Based Infant Formulas, Whey-Hydrolysate Formula, and Human Milk in Weanling Rhesus Monkeys

Silvia Rudloff, MS, Bo Lönnerdal, PhD

· An adequate supply of calcium is important for normal bone mineralization in infants. Special Infant formulas have been developed to treat infants with a high risk of developing allergy. Similar to other diets, it is important that these products are nutritionally adequate. We have measured calcium retention from a new formula based on whey hydrolysate and compared it with conventional formulas, using extrinsic labeling with calcium 47 and the weanling rhesus monkey as an animal model. Retention of calcium was similar for all formulas studied: $45\% \pm 4\%$ (mean \pm SEM) from whey-hydrolysate, 47% ± 2% from whey-predominant, and 53% ± 7% from casein-predominant formula. Calcium retention from human milk, 72% ±3%, was significantly higher than from formula. Using these retention values and the calcium concentrations of the diets, infant formula and human milk deliver approximately equal amounts of calcium to the infant.

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 Γ eeding of infants with a family history of food allergies is still a controversial topic. Early introduction of cow's milk formula and therefore antigens like β -lactoglobulin, α -lactalbumin, serum albumin, or caseins could lead to a manifestation of allergy in hypersensitive infants. On the other hand, dietary cow's milk proteins may be transferred to human milk and could cause allergic reactions in breast-fed infants. One approach to decrease the allergenic potential of cow's milk formula is enzymatic in vitro hydrolysis of whey proteins before they are used as a

protein source in formula production. Whether this treatment has an effect on the nutritional value of formulas is not well known, eg, mineral and trace element absorption could be impaired since both whey proteins and caseins are known to bind minerals and trace elements and may affect their absorption in the infant's intestine. 8,9

In this study the absorption of calcium from infant formulas based on different protein sources and from a whey protein hydrolysate as well as from human milk was investigated. Food allergy usually presents during the first 6 months of life and remains a common pediatric problem during the second half-year of life and later. Since infant formula at this age is a significant part of the diet, ¹⁰ we decided to investigate calcium absorption from various diets using the weaned, 8-month-old infant rhesus monkey as an animal model.

MATERIALS AND METHODS Animals and Study Design

Six healthy weanling (7 to 8 months old) rhesus monkeys (Macaca mulatta) from the California Primate Research Center at the University of California, Davis, underwent absorption studies. Their regular diet consisted of monkey chow (Ralston Purina Co, St Louis, Mo) and water. Prior to absorption tests, the animals were weighed and then fasted for 6 hours. The monkeys were fed 20 mL of calcium 47-labeled human milk or infant formulas by gastric intubation. Animals were fed pairwise, ie, two monkeys received the same diet and were switched to another diet 7 days later until each one had received all five diets tested. Prior to intubation, monkeys were restricted in small cages and counted in a whole-body counter for background or residual counts. The counter at the laboratory for Energy-Related Health Research, University of California, Davis,

consists of two 10×20 -cm sodium iodide crystals (Harshaw/Filtrol, Solon, Ohio) connected to a multichannel analyzer (ND-66, Nuclear Data Co, Schaumburg, Ill). Animals were counted again for 5 minutes immediately after intubation, then 2.5 and 7 days after dosing to determine isotope retention. Feces were free from stool marker at 2.5 days after intubation.

This study was approved by the Animal Care and Resources Committee and by the Radiation Safety Committee at the University of California, Davis.

Radiolabeling of Diets

Fresh human milk (from a mother in the fifth month of lactation) and four commercially available infant formulas (Table) were labeled with 1.85×10^4 Bq of 47 Ca chloride (specific activity, $>740 \times 10^4$ Bq/mg of calcium) (Amersham, Arlington Heights, Ill). The radiolabel was allowed to equilibrate for 3 hours prior to intubation. FD&C blue (0.2%) was added as a stool marker. To test for equilibration of the extrinsic label, 47Ca, and native calcium, aliquots of the diet were centrifuged after 3 hours (189 000g, 4°C, 1 hour). Distribution of ⁴⁷Ca among fat, soluble, and insoluble fractions was determined using a well-type gamma counter (Gamma Counter 8500, Beckman Instruments Inc. Fullerton, Calif) and compared with the distribution of native calcium analyzed by flame atomic absorption spectrophotometry (IL 551, Instrumentation Laboratories, Wilmington, Mass).11

Colorimetric Assays for Lactose and Phosphate

Lactose was assayed according to the method of Dahlquist.¹² The phosphate content was determined using the method of Eibl and Lands.¹³

Statistics

For calculations of the whole-body retention of the radioisotope, the major ⁴⁷Ca peak at 1.31 MeV was used. Data were analyzed

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by one-factor analysis of variance (ANOVA) followed by Fisher PLSD. A significant difference between diets was taken as P<.05.

RESULTS

We used an extrinsic labeling technique for the different diets to determine calcium retention by whole-body counting. Equal distribution of the extrinsic label (**Ca) and native calcium among fat, soluble, and insoluble proteins obtained after ultracentrifugation of whole milk was achieved in whey-hydrolysate and milk-based formulas as well as in human milk. In the soy formula, however, the amount of insoluble, native calcium was higher than indicated by the extrinsic label.

Human milk and different infant formulas given to weanling monkeys as a one-time dose were well tolerated by all animals despite the fact that their regular diet was monkey chow and water only.

Calcium absorption was determined as whole-body retention of ⁴⁷Ca. At 2.5 days after intubation of radiolabeled diet, $45\% \pm 4\%$ (mean \pm SEM) of the calcium from whey-hydrolysate formula, 47% ±2% from whey-predominant formula. 53% ±7% from casein-predominant formula, and 41% ±4% from soy formula had been absorbed (Fig 1). There was no significant difference between the product based on cow's milk whev-hydrolysate (formula 1) and formula with varying casein/whey protein ratios (formulas 2 and 3) or the soy formula (formula 4). However, there was a tendency for the casein-predominant formula (formula 3) to have a positive effect on calcium absorption. When comparing infant formula with human milk, however, calcium absorption from human milk was significantly higher (P<.05) with a mean of $72\% \pm 3\%$ (Fig 1). Taking into account that the total calcium content of human milk as well as of rhesus monkey milk14 is lower than in infant formulas (Table), there were no significant differences in absolute amounts of calcium absorbed from the diets tested (Fig 2).

Even though the feces of all monkeys were cleared from dye by 2.5 days, indicating that the diet had passed the intestinal tract, the animals were counted again after 7 days for whole-body retention of 47Ca. Measurements after 7 days

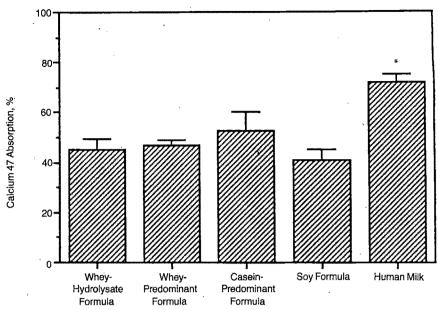


Fig 1.—Calcium 47 retention from human milk and infant formula determined by whole body counting and expressed as mean \pm SEM (vertical bar). Asterisk indicates P<.05.

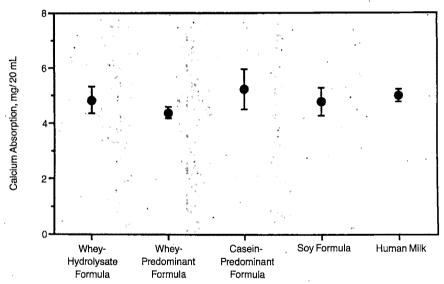


Fig 2.—Total calcium absorption calculated from calcium 47 retention (percent) and calcium content of diets (milligrams). Vertical bar indicates mean ± SEM.

demonstrated further excretion of the radioisotope to about 2%, but the relative differences among the diets remained equivalent (data not shown).

COMMENT

Calcium retention from infant formulas based on various protein sources was tested in weanling rhesus monkeys. Similarities of the gastrointestinal tract of these animals with humans¹⁵ as well as

similarities in milk composition of rhesus monkeys and humans¹⁴ make these animals an appropriate model for absorption studies in infancy.

In this study, we measured calcium retention at 2.5 and 7 days after intubation. Since the retention values were similar, it is evident that our retention values at 2.5 days are very close to true absorption values. Calcium retention from infant formulas was between 41%

Protein Sources and Lactose, Calcium, and Phosphate Levels	;
in Infant Formulas and Human Milk	

Formula No.	Product	Protein Source*	Lactose,† g/dL	Calcium,‡ mg/L	Phosphate,§ mg/L
1	Whey-hydrolysate formula (Good Start HA, Carnation, Los Angeles, Callf)	Partly hydrolyzed cow's milk whey	4.81	538	440
2	Whey-predominant formula (Enfamil, Mead Johnson, Evansville, Ind)	Whey protein/ casein (60/40)	7.04	469	526
3	Casein-predominant formula (Similac, Ross, Columbus, Ohio)	Whey protein/ casein (20/80)	7.56	494	547
4	Soy formula (Prosobee, Mead Johnson)	Soy protein	1.02	584	513
5	Human milk	Whey protein/ casein (66/34)	7.14	347	273

^{*}Protein source information was supplied by the manufacturer.

†Lactose level was determined by lactose assay.

§Phosphate level was determined by phosphate assay.

and 53%. There was no statistical difference in calcium absorption from the formula based on hydrolyzed cow's milk whey protein (formula 1) and the formula with a whey protein/casein ratio of 60/40 (formula 2). At a lower whey protein/casein ratio of 60/80, as in formula 3 (Table) and in native cow's milk, calcium absorption tended to be slightly higher. The reason for this observation could be that caseins have a high affinity for minerals and trace elements such as calcium and zinc. 16,17 It has been suggested that casein phosphopeptides derived from digestion of \beta-casein bind calcium8 and keep it in solution, therefore enhancing its bioavailability.9 However, none of the formulas tested in this study reached the absorption level from human milk, which was significantly higher than from any of the other diets. Whether casein phosphopeptides derived from human milk are more effective in promoting calcium absorption than cow's milk casein phosphopeptides from infant formulas is not known. Since infant formulas go through a process of heat treatment, it is possible that not only the configuration of proteins has changed, but also their ability to keep bound minerals in solution. In addition, cow's milk casein contains α-caseins. which are known to form complexes with calcium. 18 Since this type of casein subunit is absent in human milk, it is possible that α-casein-protein-calcium complexes may have a negative effect on calcium solubility and/or absorption. It is known that the amount of calcium in the diet influences the activation of specific calcium-binding proteins in the intestinal mucosa, and increased amounts of calcium-binding protein can be found with low-calcium diets.19 Human milk, however, with approximately 350 mg of calcium per liter, cannot be considered as low in calcium. In addition, since we used a single dose to determine calcium absorption, it is unlikely that the differences in absorption are due to an immediate adaptation of the calcium-binding protein concentration to the calcium level of the diet.

Whether the significantly lower phosphate content of human milk (Table) leads to a higher absorption of calcium by increasing serum 1,25(OH), D, levels is controversial. A correlation between calcium and phosphate absorption^{20,21} would mean that calcium absorption is higher from diets that are low in phosphate, like human milk. Other studies, however, have not found an influence of phosphate on calcium absorption. 22,28 Lactose is another factor known to have an enhancing effect on calcium absorption, possibly by increasing paracellular diffusion rates (nonsaturable transport) because of its high osmolarity.24,25 According to manufacturers' information

and our own analysis, there is virtually no difference in lactose content of human milk samples and whey- and caseinpredominant formula (Table). The lower lactose content in the whey-hydrolysate formula and the soy product is compensated for by addition of maltodextrin and corn syrup, respectively, which also increase the osmolarities of these products after being digested. They could promote mineral absorption as well, although possibly to a lesser extent than does lactose. 26,27 Ziegler and Fomon²⁶ and DeVizia et al²¹ published data from metabolic balance studies in human infants in which calcium absorption was in the same range as reported here. The lack of differences between soy formula and milk-based formula is supported by reports of a similar bone mineral content in infants fed cow's milk formula or soy formula.28 Using extrinsic labeling of the soy product might lead to an overestimation of calcium absorption from soy formula due to the fact that the extrinsic radiolabel does not completely undergo isotope exchange with part of the native calcium, presumably present as calcium phosphate or calcium phytate. Therefore, a higher proportion of the soluble calcium in sov formula becomes labeled with ⁴⁷Ca. However, while we find this in vitro, gastric acid and proteolytic enzymes may facilitate isotope exchange in vivo. That this may be true is supported by the findings of similar bone mineralization in infants fed soy formula as compared with cow's milk formula. For milk-based infant formulas, the distribution of 47Ca and native calcium was similar among milk fractions. Besides, it has been shown by Buchowski et al29 that there is no difference between extrinsic and intrinsic labeling of milk with ⁴7Ca.

It is important to note that differences in relative calcium absorption determined in this study are abolished by calculating absolute amounts of calcium absorbed (Fig 2). Therefore, statistical differences in absorption values do not reflect the capacity of different infant formula and human milk to deliver calcium to infants. This has been taken into account when establishing adequate supplementation of infant foods with minerals and trace elements. Development of a well-balanced formula is of concern, in particular for infant groups

[‡]Calcium level was determined by flame atomic absorption spectrophotometry.

^{||} Protein source was determined by densitometric scanning (585 μm) after SDS-polyacrylamide gradient gel electrophoresis and staining with Coomassie blue.

at high risk for allergy who are not breast-fed or even develop intolerances for human milk. ^{5,6} We have shown in this study using 8-month-old rhesus monkeys that, with regard to calcium absorption, all formulas investigated deliver calcium in amounts equal to human milk, although absorption of calcium from human milk is higher than from formula. This suggests that present levels of calcium supplementation would be adequate for older infants.

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Book Review

Interstitial Lung Disease in Children, volumes 1 through 3, edited by R. L. Laraga-Cuasay and W. T. Hughes, 623 pp, \$305, Boca Raton, Fla, CRC Press Inc, 1988.

This is a multiauthored series on a wide variety of lung diseases that affect children. Almost all of the authors are well known in the field of pediatric pulmonology. Unfortunately, the book's chapters are poorly integrated and reflect the multiple writing styles of the authors. Many of the topics are handled superficially. Another problem is that considerable attention is given to the discussion of obstructive airway diseases when the focus of the book is on restrictive lung diseases. Little or no attention is given to the pathogenesis of interstitial lung disease or the epidemiologic aspects of restrictive lung disease. In general, the discussions of theory are also limited. The series would have been improved if the

publication was limited to one volume that focused on interstitial lung diseases, including natural history, treatment, and unanswered research questions. It would have also been strengthened if the chapters had been better integrated.

The book may be useful as a reference guide in pediatric libraries as another compendium of pediatric pulmonary diseases. However, its price makes it prohibitive for the individual reader.

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Laboratory Evaluation of Jaundice in Newborns

Frequency, Cost, and Yield

Thomas B. Newman, MD, MPH; M. Janet Easterling; Eric S. Goldman, MD; David K. Stevenson, MD

 Neonates with hyperbilirubinemia commonly undergo a battery of laboratory tests. We used a computerized database and medical records to study the frequencv. cost, and vield of these tests in 2443 infants born at the University of California, San Francisco, between 1980 and 1982. Four hundred forty-seven (18%) of the infants met standard criteria for "nonphysiologic" hyperbilirubinemia; the incidence varied from 9% in blacks to 31% in Asian infants. About 55% of these 447 infants received a \$125 "hyperbilirubinemia workup." Hospital discharge diagnoses on all 447 hyperbilirubinemic infants were reviewed. In 214 (48%), no cause of the jaundice was identified. An additional 145 (32%) had a possible cause apparent from history, physical examination, or initial hematocrit determination. The only diagnosis made as a result of routine investigations of hyperbillrubinemia was possible ABO or Rh isoimmunization in 75 infants (17%). Nonphysiologic hyperbilirubinemia may be more common than previously reported. The recommended tests are expensive and rarely lead to diagnoses other than ABO or Rh isoimmunization. Their routine use should be reeval-

(AJDC. 1990;144:364-368)

Hyperbilirubinemia is a common problem of newborns. Traditionally, authorities have distinguished between "physiologic" hyperbilirubinemia, which is benign, and "nonphysiologic" or "pathologic" hyperbilirubinemia, which mandates further etiologic investigation. Authors of chapters in major textbooks agree1-5 that if the total bilirubin level exceeds 86 µmol/L (>5 mg/dL) on the first day of life, 171

μmol/L (10 mg/dL) on the second day of life, or 206 to 223 μ mol/L (12 to 13 mg/dL) thereafter, the bilirubinemia is (by definition) "nonphysiologic." Several laboratory tests are then recommended to determine its cause.

The expense of these recommendations has received little previous attention. The charge to the patient's family (or third-party payer) at the University of California, San Francisco, Medical Center (UCSF) for a typical "hyperbilirubinemia workup" is about \$125 (Table 1). The total cost of following published recommendations depends not only on the prices of the individual laboratory tests, but also on the frequency with which they are ordered and the cost of following up abnormal results. The potential benefit is making diagnoses that would affect treatment. This study had three major aims: (1) to determine how frequently infants of normal birth weight and different races develop nonphysiologic hyperbilirubinemia; (2) to determine how many of these infants received the recommended laboratory tests; and (3) to investigate the yield of these tests by examining hospital discharge diagnoses and procedure codes on the hyperbilirubinemic infants.

SUBJECTS AND METHODS

The study was done retrospectively, using chart reviews and a computerized database (the COmbined Patient Experience [COPE] database). The database was created by linkage of computerized data from three sources: the clinical laboratory, hospital census data, and medical record discharge abstracts. The database has been described in previous reports.6,7

The database includes patients discharged from UCSF between October 1, 1980, and September 30, 1982. We restricted our attention to infants who were born at UCSF and discharged within the 2-year period. We included only infants weighing 2500 g or more at birth; 341 (12%) of the 2784 infants were excluded because of low birth weight. We did not exclude infants with serious illnesses, because some of these illnesses might have been diagnosed based on laboratory tests ordered to evaluate jaundice.

During the study period, standard practices of neonatal care were followed. Newborns were examined at least twice daily by experienced nurses. Bilirubin levels were determined on newborns who developed jaundice in the first 24 hours after birth and on infants thought (by either nurses or house officers) to have marked jaundice thereafter. Bilirubin levels were determined in infants without jaundice only on the rare occasion that maternal antibody titers suggested a high risk of hemolytic disease of the newborn. Investigations of jaundice were at the discretion of the nursery house officer or attending physician; a firm guideline was that the cause of jaundice was investigated before phototherapy was initiated.

Bilirubin was measured on an automated chemical analyzer (Dupont Corp, Wilmington, Del) using a direct bichromatic spectrophotometric assay. The chemical analyzer was calibrated quarterly using a commercially available standard (Fisher Corp. Pittsburgh, Pa). Coefficients of variation of no more than 4.2% at a total bilirubin of 123 μ mol/L (7.2 mg/dL), and no more than 2.8% at total bilirubin of 374 µmol/L (21.8 mg/dL). were maintained on daily quality control

Nurses noted the mother's race on admission to the hospital. The infant's race was considered to be the same as the mother's.

Table 1.—Charges at UCSF for Tests Commonly Recommended to Evaluate Newborns With Jaundice*

Test	Charges, \$
Bilirubin	
Total	19.75
Direct	7. 7 5
	additional†
Complete blood cell count	21.00
Blood type	12.00
Blood group	12.00
Direct Coombs'	25.00
Reticulocyte count	19.00
Red blood cell	8.00
morphologic	
examination	
Total	124.50

^{*}UCSF indicates the University of California, San Francisco, Medical Center,

[†]The direct bilirubin determination at UCSF is \$7.75 if ordered concurrently with other analyses (eg, total bilirubin measurement); ordered alone it is \$19.75.

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unless mother and father were known to be of different races, when race was classified as "other." When race information was unavailable, race was classified as "unknown."

We obtained hospital discharge diagnoses and procedures from the COPE database. Their original source is trained medical record abstracters, who code diagnoses and procedures after each discharge using the admission history and physical, the progress notes, and the discharge summary. One of us (T.B.N.) confirmed all diagnoses of hematologic disease, hepatobiliary disease, metabolic disease, and infection (except staphylococcal skin infections) by review of the complete COPE record or the chart.

Data were analyzed with the PC-SAS program, after appropriate data files had been created from the COPE database using "awk," a pattern scanning and processing utility available in the UNIX system.

RESULTS

A total of 2443 births met the inclusion criteria for the study. The mean (±SD) birth weight of the study group was 3440 ±485 g, with an almost normal distribution truncated at 2500 g. The median length of stay was 3 days; the range was from less than 24 hours (13 infants) to 181 days. Ninety-five percent of the infants were discharged at 8 days of age or younger and 99% by 15 days of age.

At least one bilirubin determination was obtained in 1479 (61%) of the 2443 infants. Based on the definition of nonphysiologic hyperbilirubinemia as a total bilirubin of at least 86 µmol/L (5 mg/dL) at less than 24 hours of age, at least 171 µmol/L (10 mg/dL) at less than 48 hours of age, or at least 223 µmol/L (13 mg/dL) thereafter, 447 (18%) of the infants had so-called nonphysiologic hyperbilirubinemia (hereafter called simply "hyperbilirubinemia"). As others have found, 8-11 the incidence varied remarkably with race, especially after 24 hours of age (Fig 1). For example, the incidence was 31% in Asian infants compared with 9% in black infants. Racial differences were highly statistically significant ($\chi^2 = 53$; df = 6; P < .001).

How many of these infants actually had blood tests done to evaluate their jaundice? For each test, the difference in the frequency the test was ordered in infants with and without hyperbilirubinemia provides a rough estimate of how often it was ordered specifically to evaluate hyperbilirubinemia. This is a

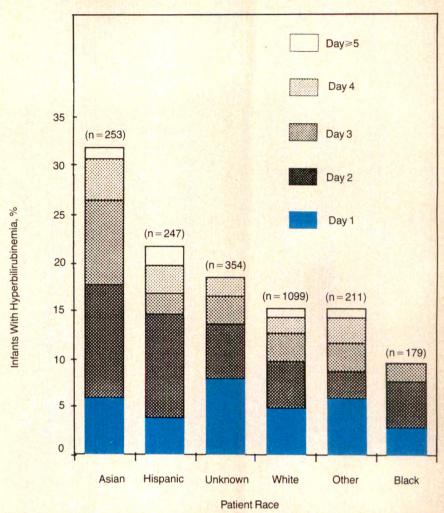


Fig 1.—Incidence of hyperbilirubinemia on different days after birth among infants of different races. Hyperbilirubinemia is defined as total serum bilirubin level of at least 86 μ mol/L (\geqslant 5 mg/dL) at less than 24 hours of age, 171 μ mol/L (\geqslant 10 mg/dL) at 24 to 48 hours of age, or 223 μ mol/L (\geqslant 13 mg/dL) thereafter.

rough estimate, because it assumes that other reasons to order these tests are equally frequent in infants who do and do not have hyperbilirubinemia. Nevertheless, consistent results emerge (Fig 2): between 50% and 60% of hyperbilirubinemic infants seem to have received a series of blood tests for hyperbilirubinemia that they would not otherwise have received.

To investigate possible benefits of these laboratory tests, we examined the discharge diagnoses on the 447 infants with hyperbilirubinemia (Table 2). One hundred forty-five infants (32%) had only diagnoses made from the history, physical examination, or the hematocrit determination done routinely at 4 hours of age. An additional 13 infants (2.9%)

had diagnoses that might have explained their jaundice, but these diagnoses were not made from the routine tests. For example, 5 children had serious bacterial infections (2 with group B streptococcal bacteremia, 2 with probable syphilis, and 1 with pneumococcal sepsis). In all 5 the infection was suspected, and appropriate tests were done before the onset of jaundice. The diagnosis of hepatobiliary disease (presumed viral hepatitis) was made in 1 patient following excessive bleeding from a heel stick, before the onset of jaundice. The diagnosis of glucose-6phosphate dehydrogenase deficiency was made in 3 patients, and galactosemia was diagnosed in 1 patient following screening for those specific disor-

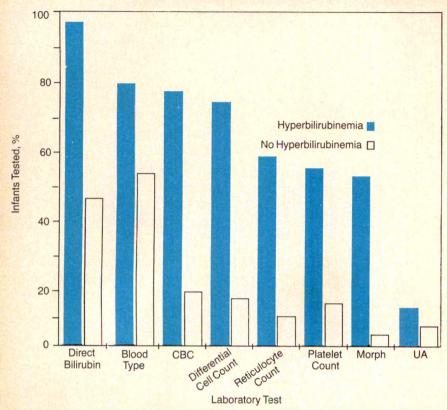


Fig 2.—Frequency of ordering of laboratory tests in infants with and without hyperbilirubinemia. Blood type represents blood type, group, and direct Coombs' test (always ordered together); CBC, complete blood cell count; Morph, red blood cell structure determined by examination of peripheral smear; and UA, urinalysis.

ders, not because of results on any of the tests in Fig 2.

The only diagnosis recorded that apparently resulted from any of the routine hyperbilirubinemia investigations was (probable) isoimmunization secondary to incompatibility of ABO blood group or Rh type, either alone (58 patients: 12.9%) or in combination with other possible causes of jaundice (17 patients; 3.8%). No firm criteria existed for this diagnosis other than marked jaundice and a blood group or type incompatibility with the mother; 32% of infants diagnosed as having isoimmunization had negative Coombs' test results. In 214 (48%) of the patients no cause of jaundice was identified.

To see how often the diagnosis of isoimmunization might affect immediate treatment, we examined the records of all patients with isoimmunization. Ten of these infants (2 with ABO disease and 8 with Rh disease) received exchange transfusions; all 10 had positive direct Coombs' test results and were

either noted to be at risk prenatally or developed jaundice at less than 24 hours of age. Thus, not surprisingly, determinations of blood type and group (and possibly the other tests for hemolysis) seem to be most useful in infants with early jaundice.

Some extrapolations and assumptions are needed to estimate the cost of the laboratory tests done to evaluate hyperbilirubinemia. The simplest approach assumes all qualifying infants would receive the recommended tests. and none of the tests would otherwise be done. Using our race-specific incidence rates, weighted by the proportion of births of each race in the United States, 12 gives an approximate total hyperbilirubinemia incidence of 15%. Although the charge for the recommended battery of tests is about \$125 at UCSF. actual collections are considerably less, because of incomplete reimbursement from third-party payers, negotiated agreements, and bad debts. Actual collections are about 65% of billings, or

Re	e 2.—Diagnoses Possibly lated to Jaundice in 447 perbilirubinemic Infants
No. (%)	Diagnosis
C	4) Diagnosis only from history, physical examination, or initial hematocrit reading significant bruising or ephalhematoma (only) olycythemia (only)
28 F 8 Ir	orycythernia (only) Prematurity (only) Infant of diabetic mother (only) Infant of diabetic mother (only)
13 (2.9)	
3 V 3 G 1 H	Bacterial infections Firal infections Blucose-6-phosphate deficiency depatitis Balactosemia
58 (12.	
13 F 17 (3.8)	Rh isoimmunization (only) Diagnosis possibly from routine investigations, accompanied by other diagnoses
7 ls C 1 ls	soimmunization and prematurity soimmunization and bruising or ephalhematoma soimmunization and bacterial offection (group B streptococcal
s 1 ls ir 1 ls	epsis) soimmunization and viral nfection (enteroviral meningitis) soimmunization, infant of diabetic
214 (47.	nother, and cephalhematoma 8) No specific diagnosis related to jaundice

about \$80 per infant with jaundice. Multiplying this cost per infant by the proportion of infants with jaundice (15%) and the annual number of births (3.7 million) in the United States gives about \$45 million per year in the United States.

The actual amount being spent to evaluate hyperbilirubinemia may be less, because not all recommended tests are being done, or because some of them would have been ordered for other reasons. If elsewhere, as at UCSF, the tests are ordered on about 55% more infants with hyperbilirubinemia than without it, the actual excess expenditure would be about \$25 million. If our incidence of hyperbilirubinemia or our frequency of testing is atypically high, the amount spent nationally for hyperbilirubinemia evaluations is less. However, the true cost includes not only the

cost of the recommended tests, but also the cost of further evaluation of abnormal results and the cost of any additional (perhaps unwarranted) laboratory tests, such as the differential determinations and platelet count, which are being done in this setting (Fig 2). Thus, \$25 million may be a conservative estimate for current annual expenditures for hyperbilirubinemia evaluations.

COMMENT

We found that 18% of UCSF newborns met standard criteria for a \$125 "jaundice workup." Several points merit discussion. First, the race-specific incidence of hyperbilirubinemia in our study seems higher than that reported in several previous studies. 18-17 Direct comparisons are difficult, however, because ours is the first study, to our knowledge, to define hyperbilirubinemia to include bilirubin values as low as 86 µmol/L (5 mg/dL) if they were obtained on the first day after birth or 171 umol/L (10 mg/dL) on the second day after birth. Fully 68% of the hyperbilirubinemic infants in this study were so classified because of bilirubin values obtained at less than 2 days of age. If we use only a peak bilirubin of 222 µmol/L or greater (≥13 mg/dL), our incidence is 10% in whites, 4.4% in blacks, and 23% in Asians, close to that reported in other recent studies. 9,11,18,19 To estimate the cost of following published recommendations for laboratory testing, it is preferable to define hyperbilirubinemia as the authors of those recommendations define it. Our definition of hyperbilirubinemia is, if anything, a bit more restrictive than that of some authorities. 1,2

Another factor that may account for our high incidence of hyperbilirubinemia is the frequency of breast-feeding in our population. Breast-feeding leads to substantial elevation of bilirubin levels as soon as the first few days after birth. 14,18-21 As more women have elected to breast-feed, the incidence of hyperbilirubinemia has increased. Other authors have shown that the yield of hyperbilirubinemia evaluations is much lower in breast-fed infants19 and have suggested a higher "normal range" in such infants. 22,23 Our database does not include information on breast-feeding, but it does suggest that race also should be considered in the construction of normal ranges for newborns' bilirubin values.

This was a retrospective study, in which bilirubin levels were determined on selected infants with jaundice, rather than on all infants. This could not be the cause of the high frequency of hyperbilirubinemia we found. Selective bilirubin screening could cause underestimation, not overestimation, of the true incidence, because infants who did not have a bilirubin determination were assumed not to have hyperbilirubinemia in our calculations. Similarly, incomplete follow-up (due to infants being discharged at only 1 or 2 days of age) would cause only underestimation of the true incidence. For the purposes of this study, the retrospective design is preferable, because it allows us to study hyperbilirubinemia as it occurs in real life, rather than in a research setting. Infants whose hyperbilirubinemia would not have been detected had they not been part of a research study do not incur laboratory costs in the "real world," and therefore were not of interest for this study.

Selective (inpatient) bilirubin testing or early discharge from the hospital may have led to some important diagnoses being missed in our inpatient database, which were made subsequently in outpatients. We doubt that this occurred often enough to affect our results, because patients at highest risk (those with the most severe jaundice earliest in life) were most likely to be examined as inpatients. However, in subsequent studies we do plan to expand the database to include outpatient data, particularly because early discharges are becoming more frequent than they were in the study period between 1980 and 1982.

We estimate the annual cost of routine hyperbilirubinemia evaluations in the United States to be about \$25 million. This is comparable with the cost of newborn screening for phenylketonuria or hypothyroidism. For individual clinicians, what their patients have to pay for these tests may be more important than the nationwide estimates and can be determined with greater accuracy. Practitioners should familiarize themselves with charges at their own hospitals; in an informal survey of five San Francisco (Calif) Bay Area hospi-

tals, charges for the tests in Table 1 varied from \$122.75 at San Francisco General Hospital to \$279 at Stanford.

Given the substantial costs, it seems reasonable to ponder the potential benefits. Asymptomatic patients can benefit from laboratory tests if the tests lead to the diagnosis of serious illnesses for which early detection is an advantage. 27-29 The sample size of this study was not sufficient to rule out the possibility that hyperbilirubinemia evaluations might uncover uncommon (incidence <1%), serious, treatable illnesses. However, we admit considerable skepticism about the role of routine hyperbilirubinemia investigations in diagnosing such illnesses. If early diagnosis and detection were crucial, it seems unlikely that the sensitivity and specificity of jaundice and the tests to evaluate it would be sufficient. Thus, for diseases such as hypothyroidism and galactosemia, other, much more reliable screening programs have evolved.

The main yield of routine hyperbilirubinemia evaluations in this study was the (tentative) diagnosis of ABO or Rh isoimmunization. How useful is it to make this diagnosis? Finding an ABO or Rh incompatibility does not prove hemolysis, and finding hemolysis does not rule out other causes of jaundice, as shown by an infant in this study with Coombs'-positive ABO isoimmunization who also had group B streptococcal bacteremia. The main benefit is identification of infants with severe hemolysis, so they can be treated with exchange transfusion. However, all 10 infants who required exchange transfusions in this study could have been identified with a much more selective testing strategy, such as testing only those with clear maternal risk factors or jaundice in the first 24 hours after birth.

Identification of infants with milder degrees of hemolysis may be helpful because these infants are at higher risk of later anemia or severe hyperbilirubinemia. Furthermore, some evidence suggests that hyperbilirubinemia is more hazardous (and, therefore, should be treated more aggressively) in infants with hemolytic disease. ³⁰ However, it is not clear how to tell which infants have hemolysis. Certainly a blood type or group incompatibility coupled with a falling hematocrit level, positive

Coombs' test result, high reticulocyte count, and abnormal blood smear results all suggest hemolytic disease. However, the sensitivity and specificity of these tests for hemolysis are not known. When some or all of the results are normal, it is difficult to know how treatment should be affected.

A rational determination of which laboratory tests to do on infants with jaundice requires information that is unavailable: the incidence of serious, treatable illnesses in infants with varying degrees of hyperbilirubinemia, and the sensitivity and specificity of available laboratory tests for diagnosing or predicting these illnesses. We are engaged in studies to obtain this information. In the meantime, what tests should be done in full-term newborns who have jaundice but who are otherwise well?

Until more definitive data are available, we recommend a flexible response, in which clinicians order tests they find easy to interpret when nonphysiologic jaundice seems likely. All children requiring transfusion in our study had jaundice on the first day after birth, and it seems reasonable to continue to search for evidence of hemolysis in infants whose jaundice is of early onset. A hematocrit reading and Coombs' test may suffice. Additional studies, including determination of blood type and group, reticulocyte count, and blood smear, may be helpful, particularly in infants who are anemic or whose Coombs' test is positive. (The blood type should be determined in all infants of Rh-negative mothers, so that the mothers may be treated with anti-Rh immunoglobulin.)

Infants who are 24 hours old or more who have exceptionally high bilirubin levels probably also should receive at least a hematocrit determination and Coombs' test. The definition of "exceptionally high" is arbitrary but should consider race and breast-feeding. For exclusively bottle-fed infants, we suggest about 200 µmol/L (12 mg/dL) for blacks, 240 µmol/L (14 mg/dL) for whites and Hispanics, and 275 µmol/L (16 mg/dL) for Asians. We add about 35 umol/L (2 mg/dL) to these values for infants who are breast-fed. (These round numbers fall between the 90th and 95th percentiles in our data.) The higher the bilirubin level rises above these levels, the more justified are additional efforts to determine its cause.

In infants who are not anemic and whose Coombs' test is negative, the value of the additional tests for hemolysis is uncertain. These tests probably can be reserved for patients with hyperbilirubinemia of very unusual degree or duration.

Infants whose jaundice is prolonged (>7 days) or who have any signs of illness may have cholestasis and should have a determination of direct bilirubin. The usefulness of measuring direct bilirubin levels in younger, otherwise well infants with jaundice is unknown, but probably low.

We recognize that the recommendations above represent a departure from previous guidelines and that data are insufficient to make definitive statements about the utility of these laboratory tests. Whether clinicians continue to use them may depend on philosophical considerations. Some providers may continue to order these tests until evidence is better that they are useless: others may wish not to order them until evidence is convincing that they are useful. In any case, few data support the present degree of unanimity found in textbooks regarding the need for laboratory evaluation of newborns with jaundice.

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Neurologic Sequelae of Open-Heart Surgery in Children

An 'Irritating Question'

Peggy C. Ferry, MD

The last 30 years of cardiac surgery have been like an exhilarating, breathless tour of the Himalayas, with one 'last great problem' after another succumbing to the surgeon's knife. Now we must address the irritating question of what has been achieved. What kind of life can be offered to these blue and breathless mites, snatched from the jaws of death?

ANDERSON ET AL, 1987

The reduction of the cerebral complications of cardiac surgery is undoubtedly going to be of increasing importance both medically and legally over the next 5 years.

PETER SMITH, 2 1988

 As pediatric cardiac surgical techniques have improved in recent years, mortality rates have dropped and attention has turned to residual morbidity, especially neurologic sequelae. Although the majority of children undergoing openheart surgery for correction of congenital heart defects apparently emerge with no adverse consequences, a small percentage suffer permanent neurologic injury (seizures, motor disorders). Another small and not well-defined population may be left with disorders of higher cortical function, such as mental retardation or learning disabilities. A survey of six major pediatric cardiac surgery units in North America was undertaken in 1988-1989 to ascertain current approaches to the detection and management of neurologic sequelae of pediatric open-heart surgery. All units reported seeing a small but definite incidence of postoperative neurologic

symptoms, including alterations of consciousness, seizures, and localized abnormalities such as hemiparesis or delayed choreoathetoid syndromes. Postoperative neuroimaging procedures have shown a disturbing incidence of hypoxicischemic encephalopathy, unsuspected cerebral atrophy, and subdural hematomas. Pathogenesis may include factors related to preoperative brain anomalies and/or hypoxic insults, altered cerebral blood flow and metabolism during hypothermic cardiopulmonary bypass with or without total circulatory arrest, embolization, and low cardiac output states postoperatively. Further studies are needed to examine the mechanisms of injury and to develop techniques to minimize the occurrence of these sequelae, as they may be associated with life-long neurologic disability and reduced quality of life.

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Critical congenital heart disease requiring intervention in infancy has a reported incidence of 3.5 cases per 1000 live births. The majority of these critical congenital heart lesions require complex operative repair in the early years of life, accomplished with moderate to deep hypothermia and cardiopulmonary bypass (CPB) with or without total circulatory arrest (TCA).

Over 37 000 open-heart operations were performed on children under 15 years of age in the United States in 1985. 40 In a 1988 study, the trend toward increased mortality with younger age was also noted; in children undergoing open-heart surgery with CPB over 1 year of age, the mortality rate was 2.3%; under 1 year of age it was 11.8%. 5

A previous article in *AJDC* reviewed neurologic sequelae reported up to 1985. A variety of strokes, diffuse hypoxic-ischemic lesions, intracranial hemorrhages, delayed choreoathetoid syndrome, and spinal cord lesions had been reported. Since that time, cerebral infarction, additional cases of the delayed choreoathetoid syndrome, and diffuse cortical atrophy on magnetic resonance

imaging scan¹¹ have been reported. The few available follow-up studies have reported variable outcome data, some describing favorable neurologic status and others reporting some developmental lag. ¹²⁻¹⁶ Unfortunately, many confounding variables (preexisting brain malformations, lack of preoperative neuropsychological assessment, and the inherent difficulties of developmental assessment of infants and young children) make the conclusions subject to variable interpretation.

The purpose of this report is to present the results of a 1988-1989 survey of six major pediatric cardiac surgery units, to discuss possible pathogenetic mechanisms underlying neurologic sequelae following open-heart surgery, and to suggest future research strategies to improve this neurologic outcome.

A 1988-89 SURVEY OF SELECTED PEDIATRIC CARDIAC SURGERY PROGRAMS Methods

A survey of six major pediatric cardiac surgery programs throughout North America was conducted from July 1988 through June 1989 to investigate current approaches to the assessment of neurologic sequelae used in large, high-volume pediatric cardiac surgery programs. The survey was conducted during the course of a sabbatical leave and was sponsored jointly by the University of Arizona, Tucson, and the Developmental Neurology Branch, Division of Convulsive, Neuromuscular, and Developmental Disorders, National Institute of Neurological Disorders and Stroke, Bethesda, Md. Sites were chosen on the basis of: (1) the presence of

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long-standing, established pediatric cardiac surgery programs; (2) geographic diversity; and, (3) a contact person known to the author to facilitate arrangements for the visits. A protocol was developed to provide uniformity of information gathered at each site. Insofar as possible the following individuals were interviewed at each site: pediatric cardiac surgeons, pediatric cardiac anesthesiologists, operating room perfusionists, pediatric cardiologists, pediatric intensivists, pediatric neurologists, head nurses in postoperative care units, neurophysiologists /electroencephalographers, neuroradiologists, neuropathologists, and psychologists or developmental pediatricians seeing children in follow-up evaluation.

The following general program variables were reviewed at each site: demographics (geographic area, population base served), evolution and history of individual pediatric cardiac surgery programs, number of openheart surgical procedures done each year, personnel involved, anesthetic variables, CPB variables, surgical variables, and postoperative management and follow-up. The standardized forms and protocols used at each site were reviewed, including the surgical consent form, anesthetic records, perfusion checklists, intraoperative data recording forms, and intensive care unit monitoring forms. At each site the following general questions were posed: (1) What is the nature and prevalence of neurologic sequelae, both acute and chronic, seen in your institution? (2) What procedures are used to evaluate and follow up children with neurologic signs and/ or symptoms identified after cardiac surgery? (3) What are the risk factors and possible causes of neurologic damage seen after surgery? (4) What might be done to prevent or reduce the incidence of these sequelae?

The following programs were visited:
(1) Boston (Mass) Children's Hospital, Harvard Medical School; (2) Children's Hospital National Medical Center, Washington, DC; (3) Hospital for Sick Children, Toronto, Canada; (4) Texas Children's Hospital and Texas Heart Institute, Houston; (5) University of Alabama Medical Center, Birmingham; and (6) University of California Medical Center, San Francisco.

Results

All the programs visited are performing at least 200 pediatric cardiac openheart procedures per year (range, 200 to 850; mean, 451). All programs had 2 or 3 cardiothoracic surgeons and at least 3 pediatric cardiologists (range, 3 to 20; mean, 10.8).

Anesthetic variables are noted in Table 1. All programs used fentanyl anesthesia. The degree of hypother-

Table 1.—Hypothermia and Intraoperative Monitoring							
	Site						
	1	2	3	4	5	6	
Hypothermia, °C	18	12	12-15	18	24	17	
Electroencephalographic monitoring	50%	No	No	No	Yes	No	
Transesophageal echocardiography	No	No	Yes	No	No	No	

Table 2.—Cardiopulmonary Bypass Variables								
T I LIFE	Site							
	1	2	3	4	5	6		
Oxygenator	Membrane	Membrane	Bubble	Bubble	Membrane and bubble	Membrane		
Arterial filters	No	Yes	No	No	No	Yes		
Mean duration of bypass min	45	<60	60	15-30	30	15-30		
Perfusion checklist	Yes	Yes	Yes	No	Yes	Yes		

		Table 3	-Postoperat	ive Care				
	Site							
	1	2	3	4	5	6		
Location*	Pediatric cardiology ICU	Pediatric ICU	Pediatric ICU	Cardiac surgery ICU	Cardiac surgery ICU	Pediatric ICU		
Service†	Pediatric cardiology	Pediatric intensive care	Cardio- thoracic surgery	Cardio- thoracic surgery	Cardio- thoracic surgery	Pediatric intensive care		

^{*}ICU indicates intensive care unit.

[†]The service with the primary responsibility for immediate postoperative care.

	Site							
Sign	1	2	3	4	5	6		
Seizure(s)	Seen	Seen	Seen	Seen	Seen	Seen		
Prolonged loss of consciousness*	Seen	Seen	Seen	Seen	Seen	Seen		
Choreoathetoid syndrome†	Seen	Seen	Seen	Not seen	Not seen	Not seen		

^{*}Longer than 12 hours in the absence of sedation and muscle paralysis.

mia during CPB with or without TCA varied from 12°C to 24°C. Two programs used electroencephalographic monitoring, one in approximately half the cases and the other using two bifrontal electrodes only. Transesophageal echocardiography, advocated by some for use in older patients to detect air bubbles that could enter the cerebral circulation, was used in one center.

Variables relating to the CPB procedures are noted in Table 2. Although recent trends favor the use of mem-

brane oxygenators to avoid the possible increased risk of damage to blood components with bubble oxygenators, three programs use bubble oxygenators, and two programs use them exclusively. Arterial filters inserted in the CPB equipment to reduce embolization were not used in most programs. The average duration of bypass was relatively short (<60 minutes) in all centers, attesting to the adeptness of the surgeons. All programs used either low-flow, nonpulsatile perfusion techniques or TCA, de-

[†]Usually delayed in onset, 2 to 5 days after surgery.

	Site					
	1	2	3	4	5	6
Reported acute neurologic morbidity, % By pediatric neurologists	9-15	12-25	3-4	2	8-9	1-2
By cardiothoracic surgeons	1	1-2	1	No data	1-2	1-2
Neuroimaging studies Computed tomography	Performed	Sometimes performed	Performed	Performed	Performed	Performed
Magnetic resonance imaging	Not performed or unavailable	Not performed or unavailable	Performed	Not performed or unavailable	Not performed or unavailable	Performed

pending on the nature of the underlying cardiac lesion and the complexity of the surgical repair. Perfusion checklists (to minimize human error associated with CPB itself) were employed by five of six units.

Table 3 indicates the locations and services assigned primary responsibility for the immediate postoperative care of the child following surgery. Depending on the working relationships and availability of various specialists, sites and personnel varied; two units did not involve pediatric intensivists or cardiologists to any significant extent in the postoperative care of pediatric patients. These same units cared for both adult and pediatric patients in cardiothoracic surgery intensive care settings.

Table 4 shows the nature of acute neurologic findings (seen in the first week) as reported by physicians and nurses involved in postoperative care. Because many children receive heavy sedation and/or pancurounium bromide for muscle paralysis, evaluation of neurologic signs such as seizures was not possible until drug effects were no longer present. None of the programs is using continuous electroencephalographic monitoring in the postoperative period to look for clinically silent, electrographic seizure activity. All units reported seeing clinically observed seizures at some time in the postoperative period, usually after the effects of sedation and paralysis were no longer present; seizures were described as generalized tonicclonic, multifocal, or partial in nature. Prolonged loss of consciousness or failure to awaken as expected after anesthesia was also reported by all programs. The delayed (2 to 5 days) onset choreoathetoid syndrome was noted infrequently in three programs but was not seen in the three others. Other neurologic findings were also seen, such as motor weakness, hemipareses, cranial nerve abnormalities, tremor, and incoordination, though not frequently.

Table 5 shows the percentage of acute neurologic morbidity and neuroimaging evaluation as reported by different persons involved in acute postoperative care or consultation in each unit. Percentages ranged from 2% to 25% (mean, 8%). Several individuals mentioned that neurologic consultations were not always requested in children with brief seizures or a slight delay in awakening from surgery, so these incidence figures are likely to be falsely low. Depending on access and patient transportability, computed tomographic or magnetic resonance imaging scans were performed for evaluation of neurologic signs, though in many instances, children with major neurologic symptomatology were deemed too ill to transport for a neuroimaging procedure.

Long-term neurologic sequelae are being prospectively studied in one center; the others have no current plans for such follow-up. Thus, the incidence and nature of permanent significant neurologic sequelae are, as yet, unknown. Personnel interviewed at each site concur that a spectrum of sequelae is likely.

Comment

Results of this study indicate that all programs surveyed report seeing a variable, though generally small, incidence of acute neurologic symptoms in children following open-heart surgery. Not surprisingly, differences in the incidence depend on "the eye of the beholder," with child neurologists reporting more than cardiac surgeons. While many of the symptoms, such as brief seizures, may not reflect serious or permanent brain injury, "they may signal

neuropathologic substrates (such as ischemic injury, hemorrhage, infarction, or hypoxic neuronal damage) that may lead to cognitive impairments or other neurologic problems later in life.

Preexisting brain anomalies or multiple episodes of hypoxia with the potential for brain injury may occur prior to surgery. Based on previous animal and human studies and on clinical evidence from adults undergoing open-heart surgery, however, it appears most likely that the causes of brain injury in children are multiple but are primarily related to the procedure itself, with its attendant hypothermia, CPB, TCA in some, and the potential for hypoxicischemic injury, embolization, and reperfusion injury.

Under normal circumstances, cerebral vascular autoregulation is present in young infants as well as older children.18 This protective mechanism, in which the brain blood flow (60 to 130 mL per 100 g per minute) is maintained at nearly constant levels despite major changes in systemic perfusion pressures, is thought to be maintained by regulation of vasomotor tone in cerebral arteries. The extent of autoregulation varies in different brain regions and is altered or abolished by hypoxia, hypocapnia and hypercapnia, hypotension and hypertension, hypothermia, and acidosis.19 No consensus exists regarding the alterations in cerebral blood flow and autoregulation that occur during CPB or TCA. Recent studies of cerebral blood flow in adults during deep (18°C to 22°C) hypothermic CPB using xenon clearance techniques have shown that cerebral blood flow is significantly decreased (because of temperature reduction) and that autoregulation is lost.20

Recent immunohistochemical studies have shown that a predictable sequence

of brain damage occurs after ischemia, including disruption of nerve cell bodies and dendrites, seen as early as 5 minutes after injury, with progression to loss of neuronal lamination, microvacuolation, disintegration of axonal bundles, and loss of neuropil reaction after only 30 minutes.21 With subsequent reestablishment of cerebral circulation, the lesions expand, particularly during the first 3 hours but continuing for as long as 12 hours after a 30-minute period of ischemia. Ischemic anoxia as brief as 12 to 20 minutes is associated with major alterations in postischemic microvascular perfusion, with hyperemia during the early period of reperfusion followed by a "progressive, prolonged decline" in cerebral blood flow despite adequate perfusion pressures.22

Following ischemic injury, pro-oxidation products (including oxygen-free radicals) are generated, influx or release of calcium ions occurs, and a general tissue acidosis occurs with associated release of excitatory amino acid neurotransmitters. The concept of selective neuronal vulnerability has been proposed, in which delayed neuronal death may occur in response to these subsequent metabolic alterations; in particular, the loss of calcium homeostasis and irreversible damage to neuronal membranes and intracellular mitochondria. Neuroexcitatory compounds (excitotoxins) formed during acidosis, such as glutamate and aspartate, are now thought to play a major role in postsynaptic secondary brain injury following ischemia23; glutamate antagonists such as N-methyl-D-aspartate have been proposed as potential therapy. Cardiopulmonary bypass produces a generalized tissue inflammatory reaction, with elevated prostaglandins, extensive complement activation, and increased aggregation of white blood cells and platelets.24 Nonpulsatile systemic blood flow, regional blood flow alterations, protein changes, altered pharmacokinetic properties of drugs, and hemodilution also contribute to this decidedly unphysiologic "controlled form of shock."25 The adequacy of cerebral perfusion in the small infant's brain under these altered conditions remains to be determined. Ideally, perhaps, normothermic perfusion of the brain during cardiac operations might be preferred,

so that autoregulation could be preserved and the intact brain circulation could be allowed to do what it does best—ensure the integrity of the neuronal metabolism. Low-output states immediately following surgery can also occur, as the previously cooled, weakened myocardium assumes new functions for which it is unprepared.

Postoperative care techniques needed to promote adequate cardiac output may also contribute to altered cerebral hemodynamics. For example, maintenance hypocarbic alkalosis is often used routinely to reduce right-ventricular afterload.26 This in turn could lead to increased cerebral vasoconstriction and brain ischemia. Throughout many of the writings on CPB, TCA, and hypothermia, phrases such as "we accept," "in our institution," "we use," "most repairs are performed with," etc, are commonly used, based on the authors' personal beliefs, clinical experience, and anecdotal evidence, without systematic study. Hickey and Andersen²⁷ note, for example, "The safe period of circulatory arrest varies depending on local techniques and, thus, must be individually determined at each institution." The term parochial empiricism has been coined to describe this phenomenon, not rare in any aspect of medicine.28 Unfortunately, however, firm adherence to such practices has stood in the way of determining which procedure(s) might be safest in protecting the child's brain during open-heart surgery.

Another area of potential errors relates to the interpersonal variables and the effects of stress on open-heart surgery team members. Aberg29 has written, "One of the much-evaded questions within medicine is the interpersonal variability regarding surgical results, i.e. whether some individuals, i.e. surgeons and perfusionists, regularly produce better results than others." Causes of CPB accidents include environmental factors, fatigue, stress, carelessness, inadequate training, impatience, and an "adventurous spirit."30 Study of the effects of techniques for stress prevention and reduction would be valuable in providing ways of minimizing human errors.

In summary, the CPB, hypothermia, and TCA procedures that are presumably necessary for safe open-heart surgery in the pediatric age group are associated with marked alterations in cerebral perfusion and, potentially at least, in metabolism. 31,32 The effects of deep hypothermia and CPB on the intrinsic neuronal microenvironment are uncertain, but it appears unlikely that neurons and glia can emerge totally unscathed from the profound metabolic alterations that occur. The extent to which these alterations are reversible remains uncertain.

CONCLUSIONS

Is some neurologic morbidity inevitable or acceptable as "the cost of doing business" to surgically correct lifethreatening congenital heart disease? Improvement in the prevention of brain damage in children undergoing openheart surgery in the future will likely rest on further basic and clinical studies of the alterations in cerebral circulation and metabolism that occur during hypothermic CPB with or without circulatory arrest.

Children undergoing open-heart surgery in early infancy offer a unique opportunity to study the relationship between acquired cerebral lesions and subsequent neurologic outcome. Preoperative neuroimaging studies and developmental assessment could be carried out to evaluate the possibility of preexisting cerebral anomalies or injury. Studies of intraoperative cerebral functioning with various bypass techniques and surgical repairs could be considered-for example, nuclear magnetic resonance spectroscopy performed with concomitant electrophysiologic studies. 33,34 Further studies of potential modifications of bypass equipment for neonates are badly needed, as are careful long-term follow-up studies, to determine the safety of the various procedures and types of bypass currently in vogue. Another fruitful area for study would be the use of cerebral protection agents (cerebroplegia, calcium antagonists, N-methyl-D-aspartate antagonists, iron chelators, corticosteroids, barbiturates, diazepam, fentanyl, and allopurinol35-42) in situations in which there is a likelihood of prolonged arrest and hypothermia; the potential for ensuring normal brain function appears to be greater with the prevention of neuronal injury than with treatment after the

injury has occurred.

Until such studies are conducted, surgeons, parents, and pediatricians need to be aware that the child's brain is placed at risk each time he or she undergoes open-heart surgery. Also, as noted by a cardiac surgeon some years ago, "I personally regret not doing studies on these problems years ago, because it deprived us of a rare opportunity to arrive at more exact knowledge." Randomized clinical trials are essential to increase our knowledge about safe open-heart surgery in children. In essence, every child has the right to be enrolled in a clinical trial."

In conclusion, a review of the literature on pediatric cardiac surgery and data obtained during this survey led me to concur with the British cardiac surgeon, Melrose⁴⁵: "While future advances in cardiac surgery will be less spectacular than in the heady 1960's, they will be relentless and based more securely on a wealth of confirmed fact. The prospect is wonderful."

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Magnetic Resonance Imaging of the Brain in Infants and Children Before and After Cardiac Surgery

A Prospective Study

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 We assessed the morphologic findings of the brain prospectively before and after cardiac surgery using magnetic resonance imaging. There were 12 patients with acyanotic and 6 with cyanotic heart disease. There were 2 deaths, and 1 patient did not have to undergo postoperative magnetic resonance imaging. The study group consisted of 15 patients completing both the preoperative and postoperative magnetic resonance imagings. All patients in the study group underwent moderate hypothermic cardiopulmonary bypass using a nonpulsatile membrane oxygenator. The mean (±SD) cardiopulmonary bypass time was 100 ± 55 minutes. Ten of the preoperative studies were interpreted as normal. One third (5 of 15) of the patients showed ventriculomegaly and dilatation of the subarachnoid spaces on preoperative magnetic resonance images. Measurements of the preoperative and postoperative magnetic resonance images showed a postoperative increase in the bicaudate and third ventricular diameters. Four patients in the study group developed postoperative subdural hematomas. The subdural hematomas were small and caused no demonstrable mass effect on magnetic resonance imaging. One patient had a preoperative white matter infarction. There was 1 patient with a postoperative infarction.

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A dvances in the technology of open heart surgery (OHS) and cardiopulmonary bypass (CPB) have helped thousands of children with fatal or debilitating congenital heart disease (CHD) to lead active and productive lives. However, neurological dysfunction, developing in the operative or perioperative period, still limits favorable outcome in the treatment of CHD.1 The incidence of neurological deficit after OHS is reported at 7% to 9% in adults.24 The incidence in children is unknown. Subclinical changes of the brain have been demonstrated with computed tomography following cardiac operations in children, and clinically unsuspected brain infarction and gliosis have been found in autopsy studies of children with CHD. 5,6 Considering the evidence that subclinical changes occur, we studied the morphologic features of the brain prospectively before and after cardiac surgery using magnetic resonance imaging (MRI). Magnetic resonance imaging is a more sensitive technique than computed tomography for imaging brain anatomy (white and gray matter) and for identifying pathological conditions, such as edema, gliosis, infarction, and subacute parenchymal and extraaxial hemorrhages. 7,8

PATIENTS AND METHODS

Eighteen infants and children with CHD were enrolled in a prospective brain imaging study. Patients with previous OHS were excluded from the study group. There were 12 patients with acyanotic and 6 with cyanotic heart disease. The ages ranged from 17 days to 9 years. Three of 18 patients did not have postoperative MRI done and were excluded from the study. The study group consisted of 15 patients.

Brain MRIs were done the day prior to OHS and repeated in the same manner after the course of clinical recovery. All postoperative MRIs were done before discharge from the hospital. The average time interval from the preoperative to the postoperative MRI was 10 days (range, 5 days to 4 weeks). All patients in the study group underwent OHS using moderate (26°C to 28°C) hypothermic CPB with a nonpulsatile membrane oxygenator (SciMed Life Systems Inc, Minneapolis, Minn). A 37-µm filter was placed in the arterial line in all cases. Postoperative care was provided by pediatric intensive care cardiologists.

Magnetic resonance imagings of the brain were done with a 1.5-T MRI system (GE-Signa, Milwaukee, Wis). All patients had routine spin-echo MRIs in the sagittal and axial planes of the head. The scanning pulse sequences included T1-weighted, proton density, and T2-weighted images. The T,-weighted images used a repetition time of 600 milliseconds and an echo time of 20 milliseconds. The T2-weighted and proton density images were obtained at a repetition time of 2000 milliseconds and an echo time of 20 and 80 milliseconds, respectively. Fields of view for the scans ranged from 20 to 24 cm. All MRIs had a slice thickness of 5 mm and a 256×256 matrix.

Measurements in the study were obtained with the GE-Signa computer (distance measurement mode) on the preoperative and postoperative axial T₁-weighted scans. Measurements of the bicaudate diameter of the frontal horns of the lateral ventricles and the diameter of the third ventricle were done in all patients in the study group to evaluate possible ventricular change. The level of the anterior columns of the fornix and the anterior commissure and massa intermedia served as precise anatomic landmarks for the bicaudate and third ventricular measurements. The subcutaneous fat of the skull was used as an end point to measure the largest anteroposterior and biparietal dimensions. The

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Table 1.—The Ages, Congenital Heart Disease (CHD), Cardiopulmonary Bypass (CPB) Time, and Preoperative and Postoperative Interpretations of the Magnetic Resonance Imaging (MRIs) Scans

Patient No.	Age	CHD	CPB Time,	Preoperative MRI Scan	Postoperative MRI Scan
1	1 y	Ventricular septal defect	95	Normal	Ventriculomegaly
2	9 mo	Total anomalous pulmonary venous return	41	Normal	Left occipital subdural hematoma
3	5 mo	Ventricular septal defect	72	Ventriculomegaly	Increased ventriculomegaly, right frontal subdural hematoma
4	5 y	Pulmonary atresia	71	Normal	Left temporal parietal infarction
5	9 mo	Ventricular septal defect	78	Normal	Ventriculomegaly, left occipital subdural hematoma
6	2 mo	Hemitruncus	73	Normal	Ventriculomegaly
7	1 y	Tetralogy of Fallot	96	Ventriculomegaly	Increased ventriculomegaly, left temporal, sagittal sinus subdural hematoma
8	18 mo	Tetralogy of Fallot	153	Ventriculomegaly, left occipital infarction	Increased ventriculomegaly, no change in infarction
9	10 mo	Ventricular septal defect	144	Normal	Ventriculomegaly
10	9 mo	Ventricular septal defect	83	Normal	Ventriculomegaly
11	8 y	Aortic stenosis	145	Normal	Normal
12	1 y	Tetralogy of Fallot	109	Ventriculomegaly	Increased ventriculomegaly, subdural hygromas
13	9 y	Atrial septal defect	25	Normal	Normal
14	1 y	Transposition of great vessels	250	Ventriculomegaly	Increased ventriculomegaly
15	1 y	Ventricular septal defect	65	Normal	Ventriculomegaly

comparison measurements on preoperative and postoperative scans were done at the same anatomic level of the head and with the same radiopulse sequence.

The MRIs were evaluated independently by two neuroradiologists (J.R.M. and F.J.H.). One neuroradiologist evaluated the studies blindly. There was 100% agreement in the interpretation of the MRIs by the neuroradiologists. The neuroradiological evaluation of all MRIs included assessment of the gross anatomy and magnetic resonance signal characteristics of the brain, ventricular system, and extra-axial space.

Statistical analysis of the ventricular measurements of the preoperative and postoperative MRIs was done using the paired *t* test. Linear regression analysis was used to compare CPB time with ventricular diameter changes from the preoperative to the postoperative MRIs.

RESULTS

The ages, cardiac diagnoses, CPB times, and results of the radiological interpretations are summarized in Table 1. There were two intercurrent

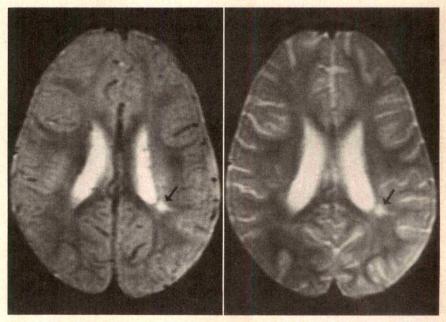


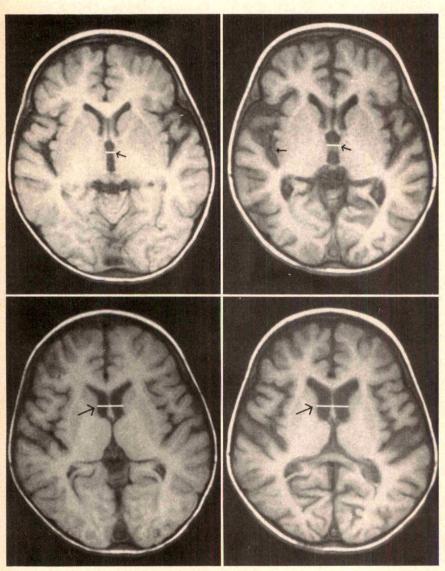
Fig 1. — Patient 8. Axial T₂-weighted magnetic resonance imaging scan. Left, Preoperative scan shows focal area of hyperintense signal in the left periventricular white matter (arrow). Right, Postoperative scan at the same level shows no change in the infarction (arrow). Note increased ventricular and sulcal volume of the subarachnoid spaces.

Table 2.—Comparison of Bicaudate Ventricular Diameter Measurements*			
	Range	Mean ± SD	
Preoperative measurements, mm	6.3-19.5	9.9±3.8	
Postoperative measurements, mm	6.6-21.9	13.0 ± 4.0	
Difference, mm	0.3-6.4	3.1 ± 1.4	

^{*}The difference shows an increase from the preoperative to the postoperative measurements (P<.005).

Table 3.—Comparison of Third Ventricular Diameter Measurements*			
Algorithms and the second	Range	Mean ± SD	
Preoperative measurements, mm	0.8-6.3	2.3±1.6	
Postoperative measurements, mm	0.9-7.9	3.9 ± 2.0	
Difference, mm	0.0-3.1	1.6±1.0	

^{*}The difference shows an increase from the preoperative to the postoperative measurements (P<.005).



deaths and one patient was unavailable for follow-up. The two deaths were of a 17-day-old infant with truncus arteriosus and an 18-month-old infant with severe tetralogy of Fallot. They were not included in the study group. The mean $(\pm SD)$ CPB time was 100 ± 55 minutes. Ten of the preoperative MRI scans were normal, but only two of the postoperative MRI scans were interpreted as normal. One third of the study group showed preoperative MRI changes of ventriculomegaly and dilatation of the subarachnoid (SA) spaces. One patient (patient 8) showed preoperative ventriculomegaly and a small focal area of hyperintense T2 signal in the deep white matter of the left occipital lobe that was interpreted as a probable previous border zone infarction. The patient had bradycardia spells and had undergone transcatheter balloon valvuloplastv 10 months before OHS. The ventriculomegaly and SA spaces increased in volume postoperatively, but the white matter infarction was unchanged (Fig 1). No border zone (watershed) infarctions were found on any postoperative MRI in the study group.

The comparison measurements of the preoperative and postoperative ventricular diameters are summarized in Tables 2 and 3. The measurements were reproducible within 0.2 mm when measured repeatedly. The measurements showed an increase in the bicaudate and third ventricular diameters (P<.005) (Fig 2). The overall anteroposterior head dimensions showed no statistical difference preoperatively vs postoperatively (t = .339, Student's t test). The biparietal dimensions had a mean preoperative measurement of 117.2 mm and a mean postoperative measurement

Fig 2.-Patient 14. Axial T,-weighted magnetic resonance imaging scan. Top left, The preoperative third ventricular diameter (arrow) is shown at the level of the anterior commissure. Note preoperative ventriculomegaly and prominent subarachnoid spaces. Top right, Postoperative scan shows increased diameter of the third ventricle (large arrow). Note overall increase in ventricular volume and cerebrospinal fluid spaces of the Sylvian (small arrow) and interhemispheric fissures. Bottom left, Preoperative bicaudate diameter (arrow). Bottom right, Postoperative scan shows increased bicaudate diameter (arrow). Note further increase in the CSF spaces of the Sylvian and interhemispheric fissures.

of 118.5 mm, with an average increase of 1.3 mm. A slight increase (1.3 mm) in the biparietal diameter is not enough to account for the observed increase in the bicaudate (mean, 3.1 mm) and the third ventricular (mean, 1.6 mm) diameters.

Four patients (patients 2, 3, 5, and 7) were found to have postoperative subdural hemorrhages (Figs 3 and 4). The subdural hemorrhages were small and caused no demonstrable mass effect on MRI. The magnetic resonance signal characteristics of the subdural hemorrhages were consistent with subacute (greater than 1 week old) hemorrhage. In addition, patient 12 showed increased ventriculomegaly and bilateral frontoparietal subdural hygromas on postoperative MRI. The hygromas showed magnetic resonance signal characteristics consistent with cerebrospinal fluid. The subdural hemorrhages were considered subclinical since no neurological sign or symptom referable to the hematomas or hygromas was reported.

Patient 4 had a normal preoperative MRI scan, but showed a left temporoparietal hyperintense T₂ signal on postoperative MRI (Fig 5). The abnormal area was interpreted as an infarction most likely due to a left middle cerebral artery embolus. The patient was found to have a right hemiparesis immediately after OHS and was the only patient in the study group with a clinically diagnosed neurological deficit.

Comparison of CPB times and the ventricular changes in diameter showed no linear correlation between the amount of ventricular enlargement postoperatively and the duration of CPB (r=.51). Excluding patient 14 (CPB time, 250 minutes), recalculation still showed no definite linear correlation (r=.59).

COMMENT

This limited neuroimaging study showed that morphological changes of the brain occurred in our group of children after recovery from OHS. Fourteen of 15 patients in the study group showed measurable increase in ventricular volumes and SA spaces. Five of 15 patients showed subclinical subdural hemorrhages on postoperative MRI. The ages of the subdural hemorrhages were consistent with occurrence during

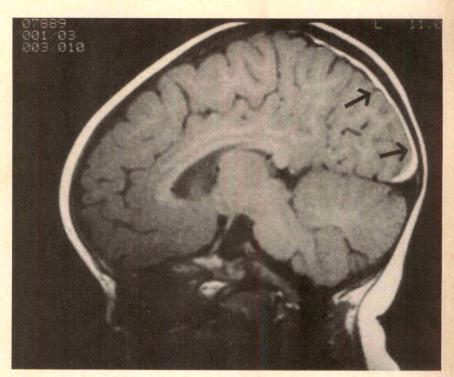


Fig 3.—Patient 5. Sagittal T_1 -weighted magnetic resonance imaging scan. Postoperative scan shows subacute hemorrhage in the subdural space over the occipital and parietal lobes (arrows).

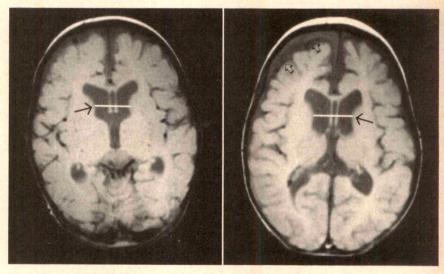


Fig 4.—Patient 3. Axial T,-weighted magnetic resonance imaging scan. Left, Preoperative scan shows bicaudate diameter (black arrow) (19.5 mm). Note preoperative ventriculomegaly and prominent subarachnoid spaces. Right, Postoperative scan shows increased bicaudate diameter (black arrow) (21.9 mm) and hyperintense subacute hemorrhage in the right frontal subdural space (open arrows).

CPB heparinization. Subclinical, as we use the term here, means that no neurological symptom or deficit was found on physical examination or that the child's neurodevelopment was not sufficiently matured to express the deficit. Patient 4, for example, showed a postoperative infarction of the left temporoparietal re-

gion, including the angular gyrus. Lesions of the angular gyrus (Gerstmann's syndrome) may be subclinical in young children before the age when writing and counting skills are usually acquired.

Patient 8 of the study group showed preoperative ventriculomegaly and a periventricular infarction in the left op-

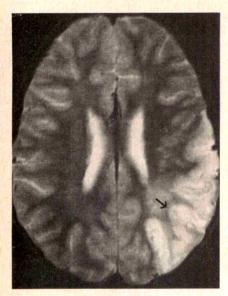


Fig 5. — Patient 4. Axial T₂-weighted magnetic resonance imaging scan. Postoperative scan shows hyperintense signal of the occipital-parietal lobe. The region of the angular gyrus and visual association cortex (arrow) is shown. Note slight increased volume of lateral ventricles and subarachnoid sulcal spaces.

tic radiations, most likely due to ischemia. There was no known visual symptom referable to the infarct, but a subclinical visual field defect could be suspected on the basis of the MRI findings. Visual defects and subtle neurological impairments are difficult to detect and assess in infants. The study also indicates that morphological changes of the brain occur before CPB operations. One third of cases in the study group had subclinical changes on MRI before surgery. These cases had severe heart disease with failure to thrive, congestive heart failure, or severe cyanosis.

All infants under 2 years of age

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showed marked ventricular enlargement and larger cisternal and sulcal SA spaces 2 to 4 weeks after CPB surgery. The measurable ventricular enlargement and dilatation of the SA spaces suggest that brain parenchymal volumes actually diminished, since there was no concomitant change in the cranial dimensions. If there is an increase in the volume of one of the intracranial compartments, such as the SA spaces and ventricles, then for the total volume to remain constant, there must be shrinkage of one of the other compartments. Communicating hydrocephalus seems an unlikely explanation for the dilatation of the ventricles and SA spaces, since there was no head enlargement or symptomatic fullness of the fontanelles in the younger patients. Re-"cerebral shrinkage" versible atrophylike pattern has been reported in association with corticosteroid therapy, Cushing's syndrome, alcoholism, severe malnutrition, and debilitating system diseases. 9-12 Changes in water content of the brain have been implicated as responsible for the "cerebral shrinkage." However, change in the water content of the brain seems an unlikely cause of the atrophylike pattern found in our study group 2 to 4 weeks after OHS.

Fluid and electrolyte balance as well as nutrition were well controlled and the circulatory hemodynamics were improved after OHS. Significant decreased global cerebral blood flow (Single Photo Emission Computed Tomography-inhaled xenon 133 method) has been observed 6 to 13 days after extracorporeal circulation. 13 The reduc-

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tion of cerebral blood flow occurred evenly throughout the brain, including the vascular border zones. In addition, cerebral blood flow (injectable ¹³⁸xenon method) measured during hypothermic nonpulsatile CPB has been shown to decline significantly during bypass surgery. ^{14,16} Further data suggest that the decline in cerebral blood flow during hypothermic nonpulsatile CPB may be secondary to cerebral microcirculatory obstruction or vasoconstriction. ¹⁶

Ischemia secondary to decreased cerebral blood flow during CPB may be a cause of the global atrophylike pattern observed in our study group. Border zone infarctions between brain areas supplied by different major arteries were not found in our postoperative group. The absence of border zone infarctions suggests that cerebral blood flow in our study group was sufficient to prevent watershed ischemia. The pathogenesis of the global atrophy-like pattern found in our series is unknown and reversibility of the phenomenon has not been established. Long-term followup neuroimaging and neurological outcome studies are planned.

This preliminary study has shown a distressing incidence of MRI brain changes in children with CHD. Considering the prevalence of subclinical changes in the brain on both preoperative and postoperative MRI scans affirms the importance of timely collaboration of pediatric cardiologists and neurologists in the management of CHD. More research is needed to assess the effects of treatment technologies on the brain and their long-term impact on the neurodevelopment of children.

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PEDIATRICIANS - Southeast United States: Sevreal progressive groups seeking board-certified or board-eligible pediatricians. Send CV to: CPR Associates, P.O. Box 235005, Montgomery, AL 36123-5005.

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GENERAL PEDIATRICIAN BC/BE - Southern California. Full-time general pediatrician to join busy multi-specialty group practice in north San Diego County. Competitive salary and fringe benefits. Send CV to: Physician Recruitment, The Mission Park Clinic, 2201 Mission Avenue, Oceanside, CA 92054. Or call: (619) 967-4892.

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Broward/Palm Beach counties; large practice; must be board-certified/-eligible. Excellent salary and benefits. Send resume to

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Professional Opportunities

LOMPOC CALIFORNIA - BC/BF pediatrician Immediate opening to join dynamic, large multispecialty clinic at branch office in Lompoc. Competitive starting salary and full benefit package. Excellent living and practice environment. Send CV to: Barbara Volk, Santa Barbara Medical Foundation Clinic, P.O. Box 1200, Santa Barbara, CA 93102

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CALIFORNIA — PEDIATRIC INTENSIVIST to join progressive thirteen-bed PICU at Huntington Memorial Hospital in Pasadena, California, a major affiliate of the University of Southern California. Excellent salary, bonus and partnership opportunities. Persons with pulmonary training are encouraged to inquire. Inquiries to: Edgardo L. Arcinue, MD, Director, PICU, Huntington Memorial Hospital, 100 Congress Street, Pasadena, CA 91105. (818) 397-8688.

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RHODE ISLAND — Solo pediatrician seeks boardeligible or board-certified associate for busy suburban private practice. Salary plus incentives leading to partnership. Full-time only. Send CV to: David P. Fletcher, MD, 300 Tollgate Road, Warwick, RI 02886.

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THE DEPARTMENT OF PEDIATRICS, William Beaumont Hospital is seeking a qualified pediatrician for the position of Chief of the Division of Developmental Pediatrics and Director of our Center for Human Development. William Beaumont Hospital is a 934-bed general hospital located 13 miles north of Detroit in Royal Oak, Michigan. We have 60 general pediatric beds, a 30-bed NICU and 6,000 deliveries annually. Our department has a staff of 120 pediatricians and 20 full-time pediatric subspecialists. We are a teaching hospital with independent residency programs in pediatrics and medicine/pediatrics affiliated with the University of Michigan and Wayne State University. Our Center for Human Development has been in operation since 1969 and sees approximately 450 new patients each year with over 4,000 patient contacts annually. The Center currently has one full-time and some part-time physicians as well as three full-time psychologists and other ancillary staff. We seek an individual with an academic background who has the clinical expertise, and administrative skills to direct and expand this program. Interested candidates should call or submit their curriculum vitae to: M. Jeffrey Maisels, MD, Chairman, Department of Pediatrics, William Beaumont Hospital, 3601 West 13 Mile Road, Royal Oak, MI 48072. (313) 551-0412.

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VIRGINIA, SHENANDOAH VALLEY — Four-physician group practice in historic community seeks fifth pediatrician BC/BE. New medical office building attached to new hospital. Contact: E.R. Caldwell, MD, Winchester Pediatric Clinic, 1330 Amherst Street, Suite C, Winchester, VA 22601. (703) 667-1727.

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NEONATOLOGIST — The Department of Pediatrics, William Beaumont Hospital is seeking a fifth full-time, academically-oriented neonatologist to join our Division of Newborn Medicine. The position involves clinical care, teaching and research. We are interested in recruiting somebody with demonstrated capability and interest in clinical and/or basic research, as well as proficiency in teaching residents. Interested individuals should submit their CV to: Daniel Batton, MD, Chief, Division of Newborn Medicine; or M. Jeffrey Maisels, MD, Chairman, Department of Pediatrics, William Beaumont Hospital, 3601 West Thirteen Mile Road, Royal Oak, MI 48072.

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NORTH CAROLINA — Charlotte Memorial Hospital and Medical Center. Two pediatric PGY-3 positions available for July 1990 in an 844-bed teaching hospital with an accredited training program. Continuity of care for general and subspecialty patients on both inpatient and outpatient services is provided. Contact: James C. Parke, Jr., MD, Department of Pediatrics, CMH & MC, P.O. Box 32861, Charlotte, NC 28232. (704) 355-3156.

PEDIATRICS — Residency position. Pediatrics, PL-III position available in fully-accredited program at the University of Florida College of Medicine. Broad inpatient and ambulatory experience in general pediatrics and all subspecialties. Completion of PL-I and PL-II years at an approved program is required. Ideal location in rapidly growing area of north central Florida with outstanding recreational opportunities. Interested individuals should contact: Lynn Kutsche, MD, Residency Director, Department of Pediatrics, JHMHC Box J-296, Gainesville, FL 32610.

Faculty Positions

GENERAL PEDIATRICIAN - The Department of Pediatrics at the University of Medicine and Dentistry of New Jersey School of Osteopathic Medicine has an opportunity for a board-eligible or board-certified general pediatrician. This is a full-time faculty position which involves teaching and clinical responsibilities. The department is well diversified. Subspecialties include a regional child abuse center, allergy/immunology, pediatric pulmonary and acute care, neonatology and genetics. Be part of this successful team of health care providers. Please send your curriculum vitae to: Martin A. Finkel, DO, Acting Chairman, Associate Professor of Clinical Pediatrics, Department of Pediatrics, University of Medicine and Dentistry of New Jersey - School of Osteopathic Medicine, Ambulatory Health Care Center, Suite #2100, (P), 301 South Central Plaza -Laurel Road, Stratford, NJ 08084. The UMDNJ is an affirmative action/equal employment opportunity employer. M/F/H/V.

NEW YORK — Division chief, general pediatrics. Department Pediatrics, State University NY at Buffalo/Children's Hospital seeks faculty member to head large general pediatrics division, with responsibility for emergency and ambulatory services. Associate professor/professor. MD, BC in pediatrics with fellowship training in general pediatrics or other pediatric subspecialty. Strong clinical, teaching and administrative skills; record of academic productivity and research interest. Send CV to: Gerald Daigler, MD, Children's Hospital, 219 Bryant Street, Buffalo, NY 14222. Equal employment opportunity/affirmative action employers.

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Faculty Positions

NEONATOLOGIST needed for Level II university-affiliated intensive care nursery in Philadelphia, Pennsylvania. Responsibilities include resident teaching, clinical duties and clinical research. Appointment to university faculty. Salary commensurate with experience. Contact: Mark Bateman, Executive Vice-President, Episcopal Hospital, Front Street and Lehigh Avenue, Philadelphia, PA 19125. (215) 427-7163.

BC PEDIATRICIAN with fellowship training in behavioral/developmental pediatrics to join the pediatric faculty at an 843-bed teaching community and regional medical center. Contact: Dr. Parke, Department of Pediatrics, Charlotte Memorial Hospital and Medical Center, P.O. Box 32861, Charlotte, NC 28232. (704) 355-3156.

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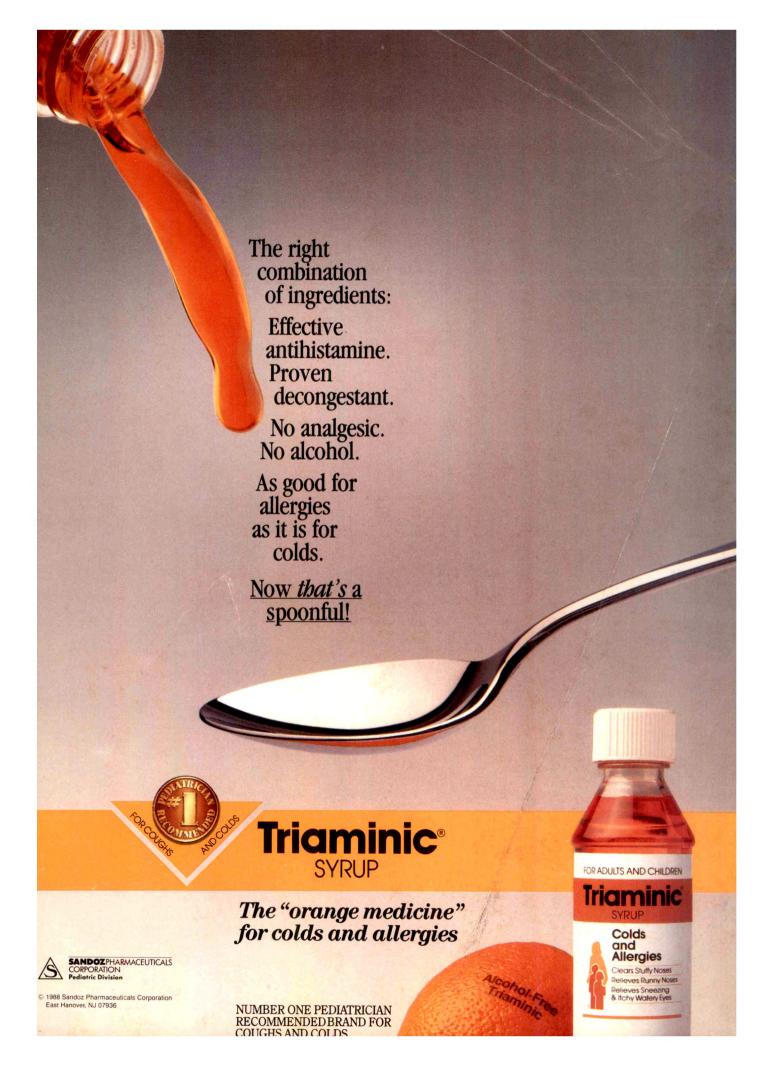
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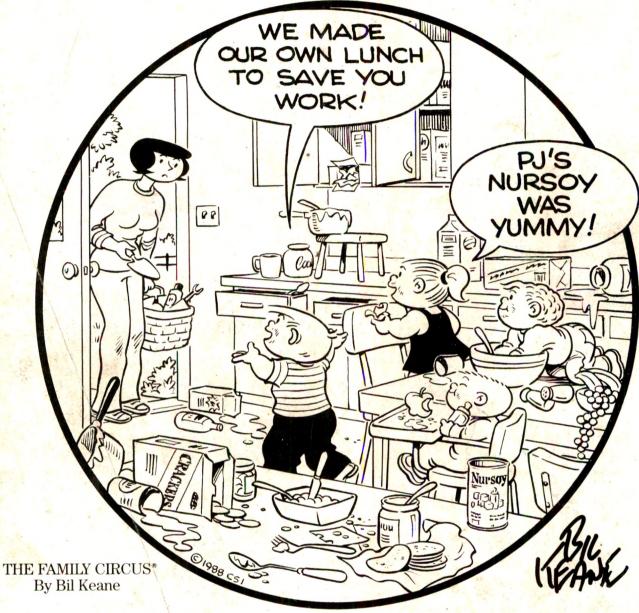
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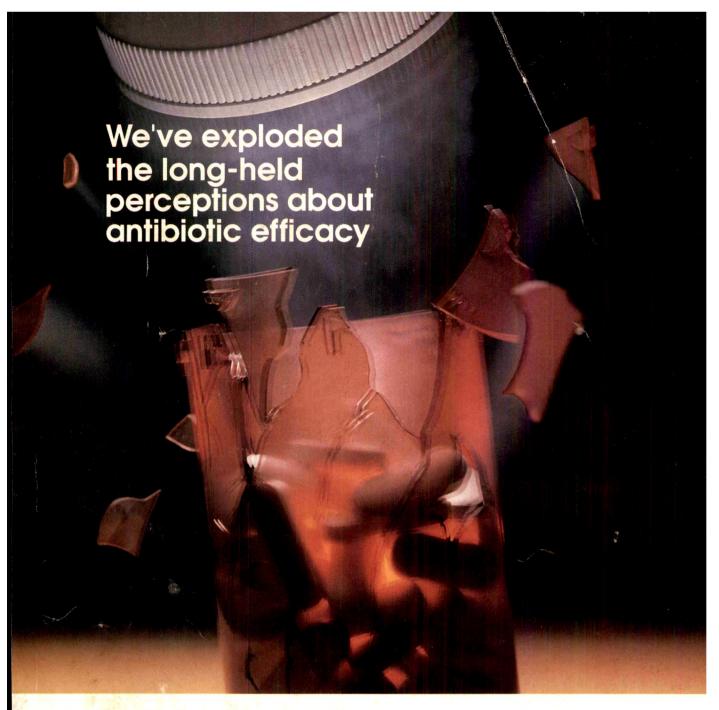
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30th Annual Meeting May 7-11, 1990 Program and Abstracts

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CLINICAL PHARMACOLLOGY

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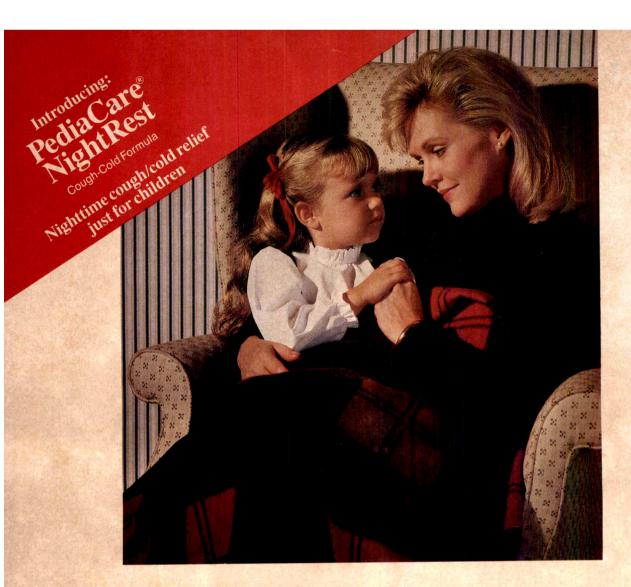


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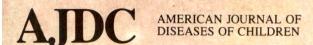
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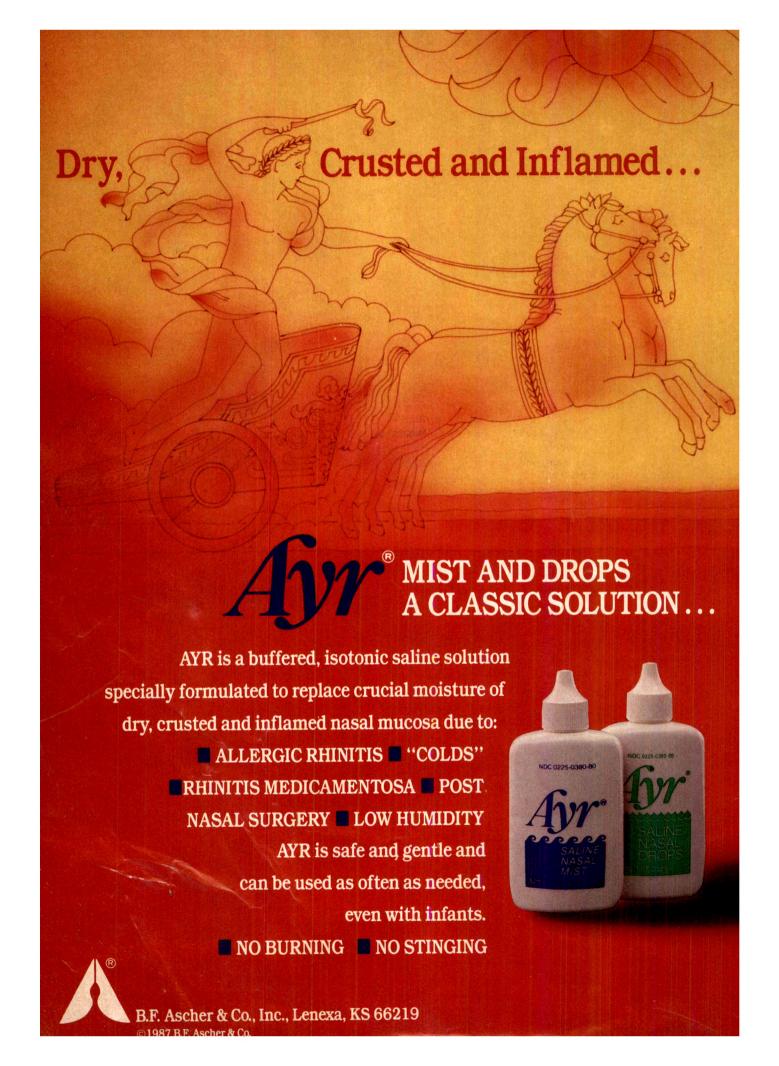
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absence of previous GI tract symptoms. In patients observed in clinical trials of several months to two
years duration, symptomatic upper GI ulcers, gross bleeding or perforation appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year.

Physicians should inform patients about the eigns and/or symptoms of serious GI trivitive and what Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration Studies to date have not identified any subset of patients not at risk of developing peptic ulceration bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

PERFAILTIONS General: Blurged and/log diminished vision, scotomata, and/or changes in color.

PRECAUTIONS: General: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If a patient develops such complaints while receiving PediaProfen, the drug should be discontinued and the patient should have an ophthalmologic examination which

includes central visual fields and color vision testing.

Fluid retention and edema have been reported in association with ibuprofen; therefore, the drug should be used with caution in patients with a history of cardiac decompensation or hypertension.

PediaProfen, like other nonsteroidal anti-inflammatory agents, can inhibit platelet aggregation, but the effect is quantitatively less and of shorter duration than that seen with aspirin. Ibuprofen has been shown to prolong bleeding time (but within the normal range) in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying hemostatic defects, PediaProfen should be used with caution in persons with intrinsic coagulation defects and those on actions and the range. anticoagulant therapy.

Patients on **PediaProfen** should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema. In order to avoid exacerbation of disease of adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ibuprofen is added to the treatment program.

The antipyretic and anti-inflammatory activity of PediaProfen may reduce fever and inflammation, thus diminishing their utility as diagnostic signs in detecting complications of presumed noninfec-tious, noninflammatory painful conditions.

Since ibuprofen is eliminated primarily by the kidney, patients with significantly impaired renal function should be closely monitored and a reduction in dosage should be anticipated to avoid drug accumulation. Prospective studies on the safety of ibuprofen in patients with chronic renal failure have not been conducted.

Safety and efficacy of Pedia Profen in children below the age of 6 months has not been established. Pregnancy: Reproductive studies conducted in rats and rabbits at doses somewhat less than the maximal clinical dose did not demonstrate evidence of developmental abnormalities. However, animal maximal clinical dose did not demonstrate evidence or developmental apriormatities. However, animal reproduction studies are not always predictive of human response. As there are no adequate and well-controlled studies in pregnant women, this drug should be used during pregnancy only if clearly needed. Because of the known effects of nonsteroidal anti-inflammatory drugs on the fetal cardiovas-cular system (closure of ductus arteriosus), use during late pregnancy should be avoided. As with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia and delayed parturition occurred in rats. Administration of PediaProfen is not recommended during pregnancy.

parturition occurred in rats. Administration of PediaProten is not recommended ourning pregnancy.

ADVERSE REACTIONS: The most frequent type of adverse reaction occurring with ibuprofen is gastrointestinal. In controlled clinical trials, the percentage of adult patients reporting one or more gastrointestinal complaints ranged from 4% to 16%.

Adverse reactions occurring in 3% to 9% of patients treated with ibuprofen: nausea, epigastric pain, heartburn, dizziness, rash. Adverse reactions occurring in 1% to 3% of patients: diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract, headache, nervousness, pruritus, tinnitus, decreased appetite, edema, fluid retention (generally responds promptly to drug discontinuation). Still other reactions (less than 1 in 100) have been reported, and are detailed in the full summary of prescribing information.

**DASAGE AMN ADMINISTRATION: Shake well prior to administration.

DOSAGE AND ADMINISTRATION: Shake well prior to administration.

Fever Reduction in Children 6 months to 12 years of age: Dosage should be adjusted on the basis of the initial temperature level (See CLINICAL PHARMACOLOGY for a description of the controlled clinical trial results). The recommended dose is 5 mg/kg if the baseline temperature is less than 102.5 °F or 10 mg/kg if the baseline temperature is greater than 102.5 °F. The duration of fever reduction is generally 6-8 hours and is longer with the higher dose. The recommended maximum daily dose is

Mild to moderate pain: 400 mg every 4 to 6 hours as necessary for the relief of pain in adults In controlled analgesic clinical trials, doses of ibuprofen greater than 400 mg were no more effective than 400 mg dose

HOW SUPPLIED: PediaProfen Ibuprofen Suspension 100 mg/5 ml (teaspoon) -

orange, berry-vanilla flavored NDC 0045-0469-04 Bottles of 4 oz (120 ml)NDC 0045-0469-16 Bottles of 16 oz (480 ml)

SHAKE WELL BEFORE USING. Store at room temperature. Caution: Federal law prohibits dispensing without prescription.

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While every precaution is taken to ensure accuracy, we cannot guarantee against the possibility of an occasional change or omission in the preparation of this index.

Instructions for Authors

NEW MANUSCRIPT PROCEDURE

On January 1, 1988, AJDC initiated a new procedure. Manuscripts submitted to AJDC will NO LONGER BE RETURNED, except in the case of accepted manuscripts or those undergoing author revision. Original artwork and photographs will be returned.

General Information. - Please send manuscripts and correspondence by first-class mail (do not use registered, certified, or express mail) to the Editor, Vincent A. Fulginiti, MD, AJDC, Dean's Office, Room 1529, Tulane University, School of Medicine, 1430 Tulane Avenue, New Orleans, LA 70112. All accepted manuscripts are subject to copy editing. The corresponding author will receive an edited typescript and layout for approval. Forms for ordering reprints are included with the edited typescript. Reprints are shipped six to eight weeks after publication. Proofs will be sent for approval if requested by the author and if printing deadlines permit. The author is responsible for all statements in his/her work, including changes made by the copy editor.

Conforming with all of the steps listed below will facilitate the editorial processing of your manuscript.

- Step 1. Cover Letter. All manuscripts must be accompanied on submission by a cover letter giving the name, address, affiliation, and telephone number of the corresponding author. The letter must include ALL of the following statements SIGNED BY ALL AUTHORS (ORIGINAL SIGNA-
- 1. Copyright Release. "In consideration of the American Medical Association's taking action in reviewing and editing this submission, the author(s) undersigned hereby transfer(s), assign(s), or otherwise convey(s) all copyright ownership to the AMA in the event that this work is published by the AMA.'
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- 3. Financial Disclosure. List all affiliations with or financial involvement in organizations or entities with a direct financial interest in the subject matter or material of the research discussed in the manuscript (eg, employment consultancies, stock ownership) OR include a statement disclaiming any such involvement. All such information will be held in confidence during the review process. Should the manuscript be accepted, the Editor will discuss with the author the extent of disclosures appropriate for publication. All accepted manuscripts become the permanent property of the publisher (AMA) and may not be published elsewhere without written permission from the AMA. After publication certain articles may appear in translation in the foreign-language edition(s) of AJDC.
- Step 2. Manuscript Format. All articles submitted should have the following features:
- 1. Four copies of the manuscript should be submitted; three are for transmission to referees and one is to be retained in the editorial office. We prefer an original and three copies.
- 2. Manuscripts should be typed in triple-spaced format on heavy-duty white bond paper, 21.6×27.9 cm (8½×11 in) with 2.5-cm (1-in) margins. Do not use justified right margins.
 - 3. Title should be no more than 75 characters.
- 4. Authors should be limited to six, all of whom have contributed to the study and manuscript preparation, are familiar with its substance, and are able to defend its conclusions.
- 5. The title page should give full names, degrees, and academic affiliations of all authors, address for request of reprints, and, if the manuscript was presented at a meeting, the organization, place, and exact date on which it was read.
- 6. Writing style should conform to proper English usage and syntax; consult the American Medical Association Manual of Style, available from Williams & Wilkins, 428 E Preston St, Baltimore, MD 21202.
 - 7. Abstract should be limited to 135 words or less.
- 8. Each table should be typed, with a title, on a separate sheet of paper, with each line, including headings, double-spaced. Continuations should be on a second sheet with all headings repeated.
- 9. Use Système International (SI) measurements throughout the manuscript.
- 10. Illustrations should be high-contrast, glossy prints, in quadruplicate, unmounted and untrimmed; lettering should be legible after reduction to column size. Figure number, name of first author, and arrow indicating "top" should be typed on a gummed label and affixed on the back of each illustration. Do not write directly on the print.

Magnification and stain should be provided for histologic sections. Fullcolor illustrations should be submitted as 35-mm, positive color transparencies, mounted in cardboard and carefully packaged. Do not submit glassmounted transparencies or color prints. Fee is \$400 for up to six squarefinished color illustrations that fit on one page. A letter of intent to pay the fee must accompany submission.

All photographs in which there is a possibility of patient identification should be accompanied by a signed statement of consent from both parents (or guardians). Covering eyes to mask identity is not sufficient.

11. References should be listed in order of their appearance in the text, type double-spaced, and in AMA format. Please follow the exact order of information and punctuation in the examples below. Note: List all authors and/or editors up to six; if more than six, list the first three and "et al."

Journal articles: Scott GB, Buck BE, Leterman JG, Bloom FL, Parks WP. Acquired immunodeficiency syndrome in infants. N Engl J Med. 1984:310:76-81.

Books: Naeye RL. How and when does antenatal hypoxia damage fetal brains? In: Kubli F, Patel N, Schmidt W, Linderkamp O, eds. Perinatal Events and Brain Damage in Surviving Children. New York, NY: Springer Verlag NY Inc; 1988:83-91.

Unpublished data, personal communications, or manuscripts "in preparation" or "submitted" should not be included in the list of references. Such material, if essential, may be incorporated in the body of the article.

Authors are responsible for the accuracy of the references.

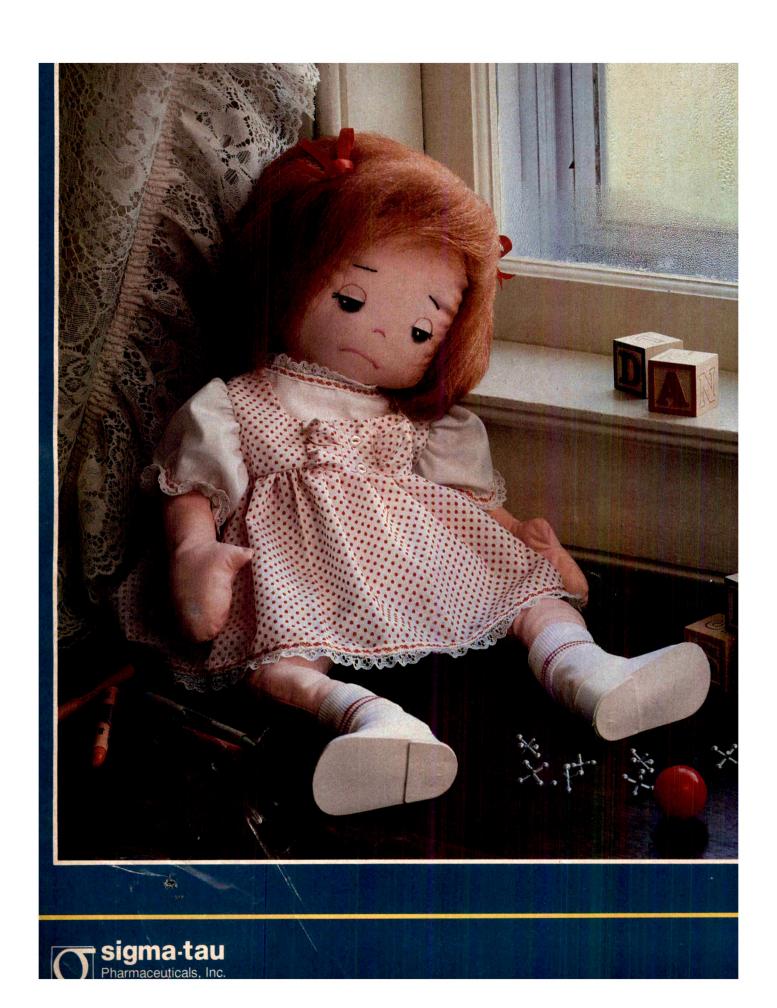
- 12. Investigations involving human subjects require a specific statement in the "Methods" section that an appropriate institutional review board approved the project and/or that informed consent was obtained from both legal guardians and/or child, if appropriate.
- 13. Illustrations and tables from other publications should be suitably acknowledged, with written permission from publisher and author. Brief acknowledgements to specific contributors directly involved in the content of the manuscript may be placed at the end of the text, before the references. General acknowledgements will be deleted.

Step 3. - Special Departments. - Criteria for several special departments are given below.

- 1. The Pediatric Forum. This is the place for comment, criticism, observations, and discussion of "issues of current concern and importance for children's health," in addition to letters that comment on articles in previous issues of AJDC. The Editor reserves the right to conduct review of and to edit all submissions. THE READER SHOULD SUBMIT TRI-PLE-SPACED COPY CLEARLY MARKED "FOR PUBLICATION" AND SIGNED BY ALL AUTHORS. REFERENCES, IF INCLUDED. SHOULD CONFORM TO THE USUAL AMA FORMAT. Copyright assignment, signed by all authors, must accompany the original submission.
- 2. From Research to Relevance. Purpose: To focus on significant research that has a high probability of being translated into clinical usefulness.
- 3. Educational Interventions. Purpose: To share information concerning any educational efforts in the broad field of pediatrics
- 4. Sports Medicine. Purpose: To provide current information related to the medical needs of young athletes, as pertinent to counseling young athletes and their parents regarding sports participation and practices contributing to the health maintenance of the athlete, as well as current concepts in the prevention, diagnosis, and treatment of sports-related illnesses and injuries.
- 5. Picture of the Month. Submissions should be sent directly to Murray Feingold, MD, National Birth Defects Center, Kennedy Memorial Hospital, 30 Warren St, Brighton, MA 02135, and should conform to the format for original articles in terms of the text, references, and illustrations.
- 6. Radiological Case of the Month. Submissions should be sent directly to Beverly P. Wood, MD, University of Rochester Medical Center, 601 Elmwood Ave, PO Box 648, Rochester, NY 14642. Submissions should conform to the format for original articles in terms of the text, references, and illustrations.

Author's Checklist

- 1. Cover letter with name, address, and telephone number of corresponding author. 2. Copyright transmittal, affirmation, and financial statements signed by ALL authors. 3. Original typed manuscript plus three copies. 4. Triple-spacing; double-spacing for tables and legends.
- 5. Right margins UNJUSTIFIED.
- 6. Title 75 characters or less.
- 7. Abstract included.
- 8. References in proper format, cited in numerical order.
- 9. Four sets of illustrations.
 - 10. Four sets of legends for illustrations.
- ____ 11. Proper consent forms for patient photographs.
- __ 12. Permission forms for illustrations previously published else-





IHE SILENI ENERGY CRISIS

Fatty acid metabolic disorders: The signs are subtle, the effects are devastating.

The lethargic, hypotonic child. The fretful infant who doesn't eat. No specific evidence of disease...yet something clearly is wrong.

Fortunately, pediatricians are now identifying a cause of these and other similarly perplexing symptoms: an inability to metabolize fatty acids. A common cause of this problem is carnitine deficiency.

Why children require adequate carnitine

Carnitine is essential for fatty-acid oxidation and synthesis in energy production. Carnitine deficiency results in loss of energy and toxic accumulations of free fatty acids. When carnitine supply is inadequate, heart and skeletal muscle activity may be severely impaired.

Severe carnitine deficiency may be associated with the following:

- hypoglycemia
- hypotonia
- hepatomegaly
- hepatic coma
- congestive heart failureneurologic disturbances
- progressive myasthenia
- letharay
- encephalopathy
- cardiomegaly
- cardiac arrest
- impaired growth and development in infants

Because oral carnitine therapy has been proven effective in primary systemic carnitine deficiency in children and because it has little or no toxicity,¹ CARNITOR® (levocarnitine) should be considered in all suspected cases of this syndrome.

So safe, there are no contraindications

CARNITOR® has no serious side effects apart from mild diarrhea, which is easily reversible with dosage adjustment or discontinuance. Because mild GI complaints have been reported, tolerance should be monitored closely during the first week and after any dosage increase.

Pediatric dosage: 50 -100 mg/kg/day of CARNITOR® Tablets or CARNITOR® (100 mg/ml) Oral Solution.



THE ONLY PRESCRIPTION FORMULATION IN TABLETS AND ORAL SOLUTION



Reference: 1. Lohninger A, Kaiser E, Legenstein E, et al: Carnitine, metabolism and function, in Kaiser E, Lohninger A (eds): Carnitine—Its Role in Lung and Heart Disorders. Basel, Switzerland, Karger, 1987, p 4.

CARNITOR® (LEVOCARNITINE)

Before prescribing, please consult complete product information, a summary of which follows:

INDICATIONS AND USAGE CARNITOR (levocarnitine) is indicated in the treatment of primary systemic carnitine

CONTRAINDICATIONS None known.

WARNINGS None

PRECAUTIONS

General CARNITOR Oral Solution is for oral/internal use General CAHNITOH Oral Solution is ro oral/internal use only. Not for parenteral use. Gastrointestinal reactions may result from too rapid consumption. CARNITOR Oral Solution may be consumed alone, or dissolved in drinks or other liquid foods to reduce taste fatigue. It should be consumed slowly and doses should be spaced evenly throughout the day (every 3-4 hours, preferably during or following meals) to maximize the practice. maximize tolerance

Carcinogenesis, Mutagenesis, Impairment of Fertility Mutagenicity tests have been performed in Salmonella typhimurium, Saccharomyces cerevisiae, and Schizosaccharomyces pombe that do not indicate that CARNITOR is mutagenic. Long-term animal studies have not been conducted to evaluate the carcinogenicity of

studies have been performed in rats and rabbits using parenteral administration at doses equivalent on a mg/kg basis to the suggested oral adult dosage and have revealed no harm to the fetus due to CARNITOR. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing mothers. Levocardition. Usage in pregnancy Pregnancy Category B Reproductive studies have been performed in rats and rabbits using

Nursing mothers Levocarnitine is a normal component of human milk. Levocarnitine supplementation in nursing mothers has not been studied.

Pediatric use See Dosage and Administration.

Pediatric use See Dosage and Administration.

ADVERSE REACTIONS Various mild gastrointestinal complaints have been reported during the long-term administration of oral L- or D, L-carnitine; these include transient nausea and vomiting, abdominal cramps, and diarrhea. Mild myasthenia has been described only in uremic patients receiving D, L-carnitine. Gastrointestinal adverse reactions with CARNITOR Oral Solution dissolved in liquids might be avoided by slow consumption or by greater dilution. Decreasing the dosage often diminishes or eliminates drug-related patient body odor or gastrointestinal symptoms when present. Tolerance should be closely monitored during first week of administration, and after any dosage increases.

carnitine overdosage. The oral LD₅₀ of levocarnitine in mice is 19.2 g/kg. Carnitine may cause diarrhea. Overdosage should be treated with supportive care. OVERDOSAGE There have been no reports of toxicity from

DOSAGE AND ADMINISTRATION

CARNITOR Tablets: Recommended adult dosage is 990 mg CARNITOR Tablets: Recommended adult dosage is 990 mg two or three times a day using the 330-mg tablets, depending on clinical response. Recommended dosage for infants and children is 50-100 mg/kg/day in divided doses, with a maximum of 3 g/day. Dosage should begin at 50 mg/kg/day. The exact dosage will depend on clinical response. Monitoring should include periodic blood chemistries, vital signs, plasma carnitine concentrations, and overall clinical condition.

overall clinical condition.

CARNITOR Oral Solution: Recommended adult dosage is 1-3 g/day for a 50-kg subject which is equivalent to 10-30 m/kday of CARNITOR Oral Solution. Higher doses should be administered only with caution and only where clinical and biochemical considerations make it seem likely that higher doses will be of benefit. Dosage should start at 1 g/day (10 ml/day), and be increased slowly while assessing tolerance and therapeutic response. Monitoring should include periodic blood chemistries, vital signs, plasma carnitine concentrations, and overall clinical condition. Recommended dosage for infants and children is 50-100 mg/kg/day which is equivalent to 0.5 ml/kg/day CARNITOR Oral Solution. Higher doses should be administered only with caution and only where clinical and biochemical considerations make it seem likely that higher doses will be of benefit. Dosage should start at 50 mg/kg/day, and be increased slowly to a maximum of 3 g/day (30 ml/day) while assessing tolerance and therapeutic response. Monitoring should include periodic blood chemistries, vital signs, plasma carnitine concentrations, and overall clinical condition. See PRECAUTIONS/General above for additional information. above for additional information.

HOW SUPPLIED CARNITOR Tablets are supplied as 330-mg, individually foil-wrapped tablets in boxes of 90. Store at room temperature (25°C). CARNITOR Oral Solution is supplied in 118-ml (4 fl oz) multiple-unit plastic containers packaged 24 per case. Store at room temperature (25°C).

CAUTION Federal (USA) law prohibits dispensing without

CARNITOR Oral Solution manufactured for Sigma-Tau, Inc. By: Barre-National, Inc., Baltimore, MD 21207-2642 Rev. 1/90

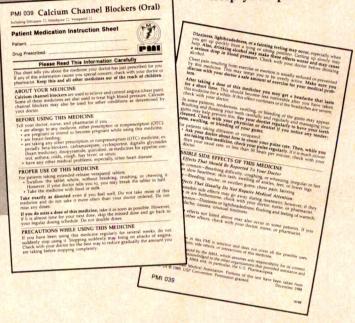




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Program and Abstracts

THIRTIETH ANNUAL MEETING
MAY 7-11, 1990
HILTON HOTEL
ANAHEIM, CA

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APA APPLICATION FOR MEMBERSHIP

Information for Prospective Members

The objectives of the Ambulatory Pediatric Association are to improve the teaching of general pediatrics, to improve research in general pediatrics, to improve patient services in general pediatrics, and to affect public and governmental opinion regarding issues vital to teaching and research in general pediatrics. Applications for membership will be considered from members of the health care professions involved in teaching and patient care or research in general pediatrics.

Application forms are obtained from the Executive Secretary's Office:

Executive Secretary
Ambulatory Pediatric Association
6728 Old McLean Village
McLean, VA 22101
(703) 556-9222

Future Annual Meetings

1991—April 29-May 3, Riverside Hilton, New Orleans, La

1992—May 4-8, Baltimore Convention Center, Baltimore, Md

1993—May 3-7, Sheraton Hotel, Washington, DC

1994—May 2-5, Seattle Convention Center, Seattle, Wash

APA PROGRAM SCHEDULE

Date and Time	Event ,	Room	Date and Time	Event	Room
Monday, May 7			9 ам-Noon	APA Topic Plenary	
6 рм-10 рм	APA Board of Di-			Sessions	
_	rectors Meeting E	El Capitan AB		Adolescent	
Tuesday, May 8		•		MedicineC	alifornia A
.8 ам-Noon	APA Board of Di-		•	Clinical Issues C	
	rectors Meeting S	San Simeon		Developmental	
		AB	•	& Behav-	
8:30 AM-9 AM	St Geme AwardF	Pacific CD	,	ioral Pediat-	
12:30 рм-4:30 рм	Clerkship Direc-			ricsC	alifornia D
4.00	torsE	El Capitan AB		Emergency	
1:30 рм-4:30 рм	APA Workshops			Medicine &	
	(1-10)	See Page 403		Child	
	APA Special Inter-			AbusePa	acific A
	est Groups			Prevention &	
	Emergency			Epidemiol-	
	MedicineL	.aguna AB		ogyPa	acific B
	International		9 ам-12:30 рм	APA General	
•	HealthS			Poster SessionC	alifornia C
	TIMO	AB	12:15 рм-1:45 рм	APA Regional	
	HMOL	a Jolla		Caairs Lun-	
	Pediatric			cheonEx	recutive
	Program	\			Board &
5 рм - 7 рм	DirectorsC APA Committee	oronado			Ante
J FINI-1 FINI	Meetings			APA Special Inter-	
	Child Health			est Group Chairs	
	Care Deliv-		0 - 5	LuncheonCo	oronado
		falibu	2 рм-5 рм	APA Workshops	
	ery			(11-21)Se	ee Page 403
	research	Room #13		APA Special Inter-	
	Serving the	H00III # 13		est Groups	
	Under-			Behavioral	. 11
	servedS	anta Monica		FellowsSa	aiinas
	EducationC	and the second s		Injury Control Co	mintrone AD
		Room #14		ControlCa	
	Public Policy E			NutritionSa Adolescent	in Clemente
		Board &		MedicineMa	anhattan
		Ante		Child AbuseSa	
	VLBWC	apistrano		AIDSLic	
		A&B	5:15 pм-7:30 pм	APA Research	10 0
7 рм-10 рм	Health Issues Re-	•	01101 M 1100 1 M	AwardPa	cific A
	search Group/			APA Teaching	omo 71
	RWJ Sponsored La	aguna A		AwardPa	cific A
Wednesday, May 9	-	_		APA Business	
7:30 ам-9 ам	APA Past Officers	•		MeetingPa	cific A
	BreakfastEl	Capitan AB		9	

APA PROGRAM SCHEDULE (con't)

Date and Time	Event	Room	Date and Time	Event	Room
Thursday, May 10			2 рм-5:30 рм	Joint Topic Ses-	
7:30 ам-9 ам	APA Regional			sions APA/APS/	
	Breakfast Meet-			SPR	
	ing			Adolescent	
	Region I	.Conference		Medicine	Pacific B
	-	Room #6		Behavioral Pe-	
	Region II	.Conference		diatrics	California A
	· ·	Room #13	:	Epidemiology	
	Region III	.Conference		& Preven-	
	-	Room #12		tive Pediat-	
•	Region IV	.Conference		rics	California B
	-	Room #2		General Pedi-	
	Region V	.Conference		atrics	Pacific A
		Room #14	5: 4 5 рм-6:45 рм	APA Armstrong	
	Region VI	Conference		Award	Pacific B
		Room #8	7:30 рм-10:30 рм	APA 30th Anniver-	
•	Region VII	Conference		sary Reception	
		Room #4		and Banquet	Pacific C
	Region VIII	Conference	Friday, May 11		
		Room #5	8:15 AM-Noon	APA General Ple-	
	Region IX	Conference		nary Session and	
•		Room #7		President's Ad-	
	Region X	Conference		dress	Pacific A
		Room #1	12:30 рм-5 рм	APA Board of Di-	
				rectors Meeting	Executive
					Board &
					Ante
9:30 ам-12:30 рм	APA Workshops			,	
	(22-31)	See Page 404	Regi	stration Hour	S
	APA Special Inter-		C		
	est Groups				
	Homeless				
•	Children				
	Day Care				
	- 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1 - 1	AB			
	Practice Man-		Friday, May 11		. 7:30 ам-Noon
	agement	Oceanside			
	Continuity		Works	hop Registrati	on
	Clinic	AVIIA A			
	Chronic	Dalianda -			
	Illness				
	Primary Care	Capistrano AB	inursday, May 10	7:	ID AM-IZ:3U PM

As an organization accredited for continuing medical education, the American Academy of Pediatrics designates this continuing medical activity as meeting the criteria for 52 credit hours in category 1 of the Physician's Recognition Award of the American Medical Association. To those currently enrolled in the American Academy of Pediatrics PREP program, this course is eligible for 52 PREP credits.

The California State Board of Registered Nursing has approved this program for 22¾ Continuing Education Credits for Registered Nurses. Certificates will be available at the APA registration desk.

AMBULATORY PEDIATRIC ASSOCIATION

1989-1990

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1961-62 Richard W. Olmsted 1962-63 Morris Green 1963-64 Robert J. Haggerty 1964-65 Frederic M. Blodgett 1965-66 Donal Dunphy 1966-67 Loren G. MacKinney 1967-68 Lewis M. Fraad 1968-69 Hugo Dunlap Smith 1969-70 Joel J. Alpert 1970-71 John H. Kennell 1971-72 Donald Fink 1972-73 Ray E. Helfer 1973-74 Katherine S. Lobach 1974-75 Evan Charney	1975-76 Frederick North, Jr 1976-77 Margaret C. Heagarty 1977-78 Robert Hoekelman 1978-79 George Comerci 1979-80 Ivan Barry Pless 1980-81 Barbara Starfield 1981-82 Alvin Novack 1982-83 Philip Nader 1983-84 Fredric D. Burg 1984-85 Abraham B. Bergman 1985-86 Catherine DeAngelis 1986-87 Jay E. Berkelhamer 1987-88 Ruth E. K. Stein 1988-89 Steven P. Shelov		
Past Secretary-Tre	easurers		
1961-1963 Frederic M. Blodgett 1963-1966 Hugo Dunlap Smith 1966-1969 Abraham B. Bergman 1969-1972 Katherine S. Lobach 1972-1974 Elizabeth S. Hillman	1974-1977 George Comerci 1977-1980 Fredric D. Burg 1980-1983 Barbara Durand 1983-1986 Marie McCormick 1986-1989 Kathleen Nelson		

THE GEORGE ARMSTRONG LECTURE

George Armstrong, an English physician of the 18th century, established the first dispensary for children in London, England, in 1769. There he served with great devotion and taught others the care of sick children. He is honored as one of the fathers of modern pediatrics, and those who deliver this lecture are also honored as outstanding teachers and contributors to our knowledge of the care of children.

The lecture is sponsored by Ross Laboratories, Columbus, Ohio.

1967 1968	George A. Silver Allan M. Butler	1976 1977	Abraham B. Bergman Wilbur J. Cohen	1984	Victor Vaughan Waldo Nelson
	Robert H. Haggerty		Richard W. Olmsted	1985	Gerold L. Schiebler
	Julius B. Richmond		John H. Kennell		Marian Wright Edelman
1971	Morris Green	1980	OXFAM (Tim Lusty)		(Children's Defense Fund)
1972	Henry K. Silver	1981	Benjamin Spock	1987	Robert A. Hoekelman
1973	Barbara M. Korsch	1982	Evan Charney	1988	Ivan Barry Pless
1974	Lewis Fraad	1983	Barbara Starfield	1989	Joel J. Alpert
1975	C. Henry Kempe			1990	Catherine DeAngelis

APA TEACHING AWARD

The purpose of this award is to foster interest in the teaching of ambulatory pediatrics by giving national recognition to an outstanding ambulatory pediatric program. Programs must demonstrate excellence in educational teaching methods, acceptance by students and/or residents, acceptance by the community and the institution, innovations and adaptability, or outstanding quality of the individuals trained in the program. Emphasis is placed on the award being given to an outstanding program.

University of Arizona		University of Arizona	1988	Emergency Room Teaching
_		_		Program
				Children's Hospital of
	1981	Sinai Hospital of Baltimore		Philadelphia (Pa)
Pediatrics		Pediatric Residency Training		and
Tucson		Program		Behavioral and
University of Chicago	1982	Child Health Associate		Developmental
Pritzker School of Medicine		Program		Pediatric
Wyler Children's Hospital		University of Colorado		Fellowship
Division of Ambulatory		Health Sciences Center		Program
Pediatrics		Denver		Ohio State University
University of Vermont	1934	University of North		Department of Pediatrics
College of Medicine		Carolina—Chapel Hill		Columbus
Department of Pediatrics		Department of Pediatrics	1989	Primary Care Training
Division of Ambulatory		Community Outreach		Program
Pediatrics		Training Program		University of California—
Burlington, Vt	1986	Pediatric Practice Model		San Diego Department of
Children's Hospital of		University of Oklahoma		Pediatrics
Philadelphia		College of Medicine		Division of General Pediatrics
Division of Ambulatory		Oklahoma City	1990	Behavioral Science
Services	1987	Chronic Illness Teaching		Training Program
Resident Group Practice		Program		Department of
Primary Care Training		Department of Pediatrics and		Pediatrics
Program		Human Development		University of California—
Department of Pediatrics		Michigan State University		San Francisco
•		East Lansing		
	College of Medicine Department of Pediatrics Division of Ambulatory Pediatrics Tucson University of Chicago Pritzker School of Medicine Wyler Children's Hospital Division of Ambulatory Pediatrics University of Vermont College of Medicine Department of Pediatrics Division of Ambulatory Pediatrics Burlington, Vt Children's Hospital of Philadelphia Division of Ambulatory Services Resident Group Practice Primary Care Training Program	College of Medicine Department of Pediatrics Division of Ambulatory 1981 Pediatrics Tucson University of Chicago 1982 Pritzker School of Medicine Wyler Children's Hospital Division of Ambulatory Pediatrics University of Vermont 1934 College of Medicine Department of Pediatrics Division of Ambulatory Pediatrics Burlington, Vt 1986 Children's Hospital of Philadelphia Division of Ambulatory Services 1987 Resident Group Practice Primary Care Training Program	College of Medicine Department of Pediatrics Division of Ambulatory Pediatrics Tucson University of Chicago Pritzker School of Medicine Wyler Children's Hospital Division of Ambulatory Pediatrics University of Vermont College of Medicine Department of Pediatrics Division of Ambulatory Pediatrics University of Vermont College of Medicine Department of Pediatrics Division of Ambulatory Pediatrics Burlington, Vt 1986 Pediatric Practice Model University of Oklahoma College of Medicine Oklahoma City Services Primary Care Training Program Department of Pediatrics and Human Development Department of Pediatrics Michigan State University	College of Medicine Department of Pediatrics Division of Ambulatory Pediatrics Tucson 1981 Sinai Hospital of Baltimore Pediatric Residency Training Program University of Chicago Pritzker School of Medicine Wyler Children's Hospital Division of Ambulatory Pediatrics University of Vermont College of Medicine Department of Pediatrics Division of Ambulatory Pediatrics University of Vermont College of Medicine Department of Pediatrics Division of Ambulatory Pediatric Practice Model University of Oklahoma College of Medicine University of Oklahoma College of Medicine Division of Ambulatory Services 1987 Chronic Illness Teaching Program Department of Pediatrics and Human Development Department of Pediatrics Michigan State University

APA RESEARCH AWARD

The APA Research Award acknowledges the contribution of an individual in advancing pediatric knowledge through excellence in research. Research excellence is characterized by originality, creativity, and methodological soundness. The findings should contribute significantly to the general health of children in such areas as understanding mechanisms of health and disease, methods of education, and innovative ways of providing children's services.

1990 Barbara Starfield

APA WORKSHOPS AND SPECIAL INTEREST GROUPS

Tuesday, May 8, 1990

1:30 рм-4:30 рм

 3. 4. 	Childhood Obesity: Treat Early and Often	Current Research, Treatment, and Policy Issues
5.	Leaders: L. L. Davidson and D. F. Schwarz Teen-Tot and Parent Enrichment: A Two-Pronged Attack to Enhance the Parenting Abilities of the Adolescent Parent	and Outcomes in Primary Care and Behavioral Pediatrics
	Evaluation and Treatment of the Multiply Handicapped Child With Acute Symptoms	Clerkship Directors (starts at 12:30)El Capitan ABEmergency MedicineLaguna ABInternational HealthSan Simeon ABHMOLa JollaPediatric Program DirectorsCoronado
	Wednesday, 2 _{PM} -	
		O F W
11.	Implementing the Principles of the GPEP Report	10 A Track-1 Ctatistical Casternas Dealers for the
12.	in a Pediatric Clerkship	18. A Useful Statistical Software Package for the Clinical Researcher
12. 13. 14.	in a Pediatric Clerkship	Clinical Researcher
12. 13. 14.	in a Pediatric Clerkship	Clinical Researcher
12. 13. 14.	in a Pediatric Clerkship	Clinical Researcher
12. 13. 14. 15.	in a Pediatric Clerkship	Clinical Researcher
12. 13. 14. 15.	in a Pediatric Clerkship	Clinical Researcher

APA WORKSHOPS AND SPECIAL INTEREST GROUPS

Thursday, May 10, 1990 9:30 AM-12:30 PM

22.	Faculty Development Workshop: Interpersonal
	Process Recall and Clinical Problem Solving in the
	Teaching and Evaluation of Medical Students and
	(House Staff) Carmel
	Leaders: A. Scheiner and B. Siegel
23.	Wound Management for the Pediatrician:
	Abrasions to Z-Plasty Redondo
•	Leaders: I. S. Landsman, L. S. Fitzmaurice, and
	J. F. Knapp
24.	Making the Acute Care Setting
	'User-Friendly' El Capitan A
	Leaders: J. R. Avner, G. R. Schwartz, S. M. Selbst,
	and S. Ludwig
25.	HIV in the Pediatric Emergency Department:
	Presentations and Precautions Manhattan
	Leaders: H. Adam, L. Bernstein, E. Crain,
	S. Cunningham, D. Dorfman and M.
	Metrou
26.	The Prevention, Diagnosis, And Treatment of
	Running Injuries Avila B
	Leaders: G. L. Landry and W. A. Primos
27.	Organizing Effective Community Child Injury
	Prevention ProgramsMonterey
:	Leaders: A. B. Bergman, F. P. Rivara, L. W. Rogers,
	and A. Young

28.	Design and Analysis of Case-Control
	Studies San Clemente
	Leaders: T. B. Newman and M. S. Kramer
29.	A Course on Enhancing One's Presentation
	Skills La Jolla
	Leaders: D. M. Super, R. E. Marshall, and
	J. M. Cullen
30.	Child Development, Pain, and Mental
	ImageryCoronado
	Leaders: R. Solomon and C. Saylor
31.	Issues in Environmental Toxicology for the
•	Pediatrician Malibu
	Leaders: A. D. Woolf, M. Shannon, and J. Graef

Special Interest Groups

Homeless Children	El Capitan B
Day Care	San Simeon AB
Practice Management	Oceanside
Continuity Clinic	Avila A
Chronic Illness	Palisades
Primary Care	Capistrano AB

APA TOPIC PLENARY SESSIONS

Wednesday, May 9, 1990 9 AM-Noon

ADOLESCENT MEDICINE AND PEDIATRIC EDUCATION

California A

Moderators: Larrie Greenberg, MD, and Modena Wilson, MD

O:00 Urinary Leukocyte Esterase Screening for Asymptomatic Sexually Transmitted Disease in Adolescent Males. M. J. Werner and F. M. Biro, Division of Adolescent Medicine, Children's Hospital Medical Center, Cincinnati, Ohio.

9:15 Intergenerational Transmission of School-Age Parenthood. S. M. Horwitz, L. V. Klerman, H. S.

Kuo, and J. F. Jekel. Departments of Epidemiology and Public Health, Yale University, New Haven, Conn.

- 9:30 The Effects of Prenatal Social Support on Infant Birthweight and Parturition for Nulliparous Teen Mothers: A Prospective Study. J. M. Pascoe. Department of Pediatrics, University of Wisconsin, Madison.
- 9:45 Does Acne Affect Adolescents' Self-Concept?
 D. Krowchuk, T. Stanein, R. Keskinen, R. Black,
 J. Bass, and T. Anglin. Departments of Pediatrics
 and Dermatology, Case Western Reserve University School of Medicine at MetroHealth Medical
 Center, Cleveland, Ohio.

- 10:00 The Effect of a Weight Management Program on Self Esteem and Body Image in Obese Youth.
 E. D. Willis, B. McCoy, and M. Berman. Department of Pediatrics, Children's Hospital of Philadelphia (Pa).
- 10:15 Chlamydia Cervical Infection in Adolescents: A Prospective Longitudinal Follow-up Observation. M. K. Oh, R. A. Feinstein, M. Rouse, O. Bermudez, B. J. Foch, and R. F. Pass. Department of Pediatrics, University of Alabama at Birmingham
- 10:30 Pediatricians' Choices to Work Full-Time (FT) or Part-Time (PT). N. Fritz and J. Lantos. Departments of Pediatrics and Clinical Ethics, University of Chicago (Ill) School of Medicine and La Rabida Children's Hospital and Research Center, Chicago.
- 10:45 Fitness, Body Fat and Perceived Stress in Residents. M. Gutgesell, A. Weltman, C. Sowa, R. Seip, A. Bulatovic, and S. Woodson. Schools of Medicine and Education, University of Virginia, Charlottesville.
- 11:00 A Computer-Assisted Intervention to Improve the Management of Childhood Asthma. J. L. Lauby, D. H. Rubin, and L. J. Bauman. Department of Pediatrics, Preventive Intervention Research Center and Division of Pediatric and Perinatal Epidemiology, Albert Einstein College of Medicine, Bronx, NY.
- 11:15 Learning by Teaching: A Resident-Taught Parent Education Oral Therapy Program for Diarrhea Implemented in a Continuity Clinic Setting. L. R. First, R. Lauerman, T. Fenton, L. Herzog, and J. D. Snyder. Department of Pediatrics, Harvard Medical School and The Children's Hospital, Boston, Mass.
- 11:30 Maternal Understanding of Commonly Used Medical Terms in a Pediatric Setting. B. L. Gablehouse and B. A. Gitterman. Department of Pediatrics, Denver (Colo) Health and Hospitals and University of Colorado Health Sciences Center, Denver.
- 11:45 Does Physician Attire Influence Parent Satisfaction With Medical Care? R. Pantell, R. Palmer, L. Sharp, C. Lewis, and A. Feldman. Department of Pediatrics, University of California, San Francisco.

CLINICAL ISSUES

California B

Moderators: Anthony Alario, MD, and Steven P. Shelov, MD

9:00 Outpatient Management of Febrile Infants (FI) 28 to 90 Days of Age With Intramuscular Ceftriaxone (CTX). M. N. Baskin, G. R. Fleisher, and

- E. J. O'Rourke. Divisions of Emergency Medicine and Infectious Diseases, The Children's Hospital, Boston, Mass.
- 9:15 Lack of Efficacy of Short-term Prednisone, Trimethoprim-Sulfamethoxazole, Alone or Combined, in Persistent Otitis Media With Effusion: Season of Entry as Possible Determinant of Outcome. C. Hearey, J. Hokanson, H. Ury, C. Chang, B. Coplan, and M. Hall. Departments of Pediatrics, Kaiser Permanente Medical Centers, Martinez, Walnut Creek, and Fremont, Calif.
- 9:30 Predictive Value of the Differential Leukocyte
 Count in Diarrheal Illnesses in Children.
 N. Schonfeld, J. Schunk, M. Amis, and J. Hirshon.
 Department of Pediatrics, Children's Hospital of
 Los Angeles (Calif).
- 9:45 The Association Between Infant Weight Gain and Breast Milk Intake Measured by Office Test-Weights. M. R. Neifert, J. M. Seacat, S. M. De-Marzo, and D. A. Young. Lactation Program, Women's Hospital at AMI Saint Luke's, Denver, Colo.
- 10:00 How Do Practicing Pediatricians Manage Febrile Infants? R. Pantell and R. Black. The California Office Based Research Group and Departments of Pediatrics, University of California, San Francisco.
- 10:15 A Randomized Controlled Trial of Cefixime Compared to Amoxicillin for Treatment of Acute Otitis Media. C. E. Johnson, S. A. Carlin, D. M. Super, J. M. Rehmus, D. G. Roberts, N. C. Christopher, and J. K. Whitwell. Department of Pediatrics, Case Western Reserve University at MetroHealth Medical Center, Cleveland, Ohio.
- 10:30 Cost/Benefit and Procedure/Benefit Analysis of Infants at Risk for Occult Bacteremia. M. Stephan, R. C. Baker, and J. C. Bausher. Department of Pediatrics, University of Cincinnati (Ohio), College of Medicine, Children's Hospital Medical Center.
- 10:45 Strategies for Diagnoses and Treatment of Occult Bacteremia: Clinical and Cost-Effectiveness. T. A. Lieu, G. R. Fleisher, D. M. Jaffe, and J. S. Schwartz. Department of Pediatrics, University of Pennsylvania, Philadelphia.
- 11:00 Predictors of Bacterial Illness in Febrile Four-to-Eight Week-Old Infants. J. R. Avner and M. D. Baker. Divisions of General Pediatrics, Emergency Medicine, and Infectious Diseases, The Children's Hospital of Philadelphia (Pa).
- 11:15 Occult Abdominal Injuries in Childhood. R. Saladino and G. Fleisher. Division of Emergency Medicine, The Children's Hospital, Boston, Mass.
- 11:30 Dog Bites in Urban Children: It's The Pits! J. R. Avner and M. D. Baker. The Division of General Pediatrics, Emergency Medicine, The Children's Hospital of Philadelphia (Pa), and the University of Pennsylvania School of Medicine, Philadelphia.

11:45 Intramuscular vs Intravenous EDTA for Lead Mobilization Testing. J. T. Kassner, M. W. Shannon, and J. Graef. Department of Medicine, Harvard Medical School, Children's Hospital, Boston, Mass.

DEVELOPMENTAL AND BEHAVIORAL PEDIATRICS

California D

Moderators: Lindsey Grossman, MD, and Lucy Osborn, MD

- 9:00 Effects of Cocaine Exposure During Gestation on Newborn Neurobehavioral Functioning. E. Anisfeld, D. Wagner, N. Ruesch, L. Ferrari, and N. Cunningham. Department of Pediatrics, Columbia University College of Physicians and Surgeons, New York, NY.
- 9:15 Antihistamines: Do They Affect Children's Performance? A. Shanon, W. Feldman, L. Leiken, A. Ham Pong, R. Peterson, and S. Raman. Departments of Pediatrics and Psychology, Children's Hospital of Eastern Ontario; Department of Epidemiology, University of Ottawa (Canada).
- 9:30 Psychological Sequelae of Medical Complications During Pregnancy. J. A. Burger, B. W. C. Forsyth, J. M. Leventhal, P. J. Leaf, and S. M. Horwitz. Departments of Pediatrics, Epidemiology, and Public Health, Yale University School of Medicine, New Haven, Conn.
- 9:45 Acculturation and Compliance With Medical Therapy in Puerto Rican Children With Asthma.

 L. M. Pachter and S. C. Weller. Division of General Pediatrics, The Children's Hospital of Philadelphia, University of Pennsylvania School of Medicine.
- 10:00 Factors Motivating Foster Parenting of Chronically Ill Children. D. Brazdziunas, C. Gosselink, A. Kresheck, and E. Ekwo. La Rabida Children's Hospital and Research Center and Department of Pediatrics, University of Chicago (Ill).
- 10:15 A Novel Asthma Camp Intervention for Child-hood Asthma Among Urban Blacks. S. B. Fitz-patrick, S. Coughlin, J. Chamberlin, and the Pediatric Lung Committee of ALADC. Pediatric Pulmonary Medicine, Georgetown University School of Medicine and the American Lung Association, Washington, DC.
- 10:30 Neurodevelopmental Outcome in Infant Cardiac Transplantation: The First Four Years. R. F. Trimm, S. Ashwal, D. M. Rincon, and L. L. Bailey. Departments of Pediatrics and Surgery, Loma Linda (Calif) University School of Medicine.
- 10:45 Causes of Decreased Linear Growth Among Homeless Children. C. D. Courtlandt, B. P. Dreyer, A. H. Fierman, W. Berkowitz, W. S. Hoover, M. Arbel, and S. D. Taylor. Department of

- Pediatrics, New York (NY) University School of Medicine.
- 11:00 Growth and Development in Children of Cocaine Abusing Mothers. E. Davis and I. Fennoy. Department of Pediatrics, Harlem Hospital, Columbia University, New York, NY.
- 11:15 Prevalence of Home Telephone Service Among Families Using an Inner-City Hospital's Outpatient Services. L. S. Wissow and M. A. Warshow. Department of Pediatrics, The Johns Hopkins University School of Medicine, Baltimore, Md.
- 11:30 Can You Spoil an Infant? A Primary Care Survey.
 R. Solomon and K. Martin. Department of Pediatrics, Medical College of Pennsylvania, Allegheny General Hospital, Pittsburgh; Department of Pediatrics and Human Development, Michigan State University, East Lansing.
- Diagnosis of Attention Deficit Hyperactivity
 Disorder (ADHD) by Primary Care Physicians.
 M. Wolraich, S. Lindgren, A. Stromquist, C. Davis,
 R. Milich, and D. Watson. Department of Pediatrics. University of Iowa, Iowa City.

EMERGENCY MEDICINE AND CHILD ABUSE

Pacific A

Moderators: David Jaffe, MD, and Stephen Ludwig, MD
9:00 Relapse Following Emergency Room (ER)
Treatment for Acute Childhood Asthma: Can It
Be Predicted or Prevented? F. M. Ducharme and
M. S. Kramer. Departments of Pediatrics and
Epidemiology and Biostatistics, McGill University
Faculty of Medicine, Montreal, Canada.

- 9:15 Upright or Lying Down: Is One Better for Doing a Lumbar Puncture (LP)? M. Lehmann, S. Gordon, A. Saulys, L. Dinnies, J. Berkelhamer, and E. Ekwo. Department of Pediatrics, The University of Chicago (Ill).
- 9:30 Increased Blood Lead in Children With Nasal, Aural or Esophageal Foreign Bodies. J. F. Wiley II, F. M. Henretig, and S. M. Selbst. Division of General Pediatrics, Emergency Medicine, The Children's Hospital of Philadelphia (Pa).
- 9:45 Ought 'Standard Care' Be the 'Standard of Care'? A Study of the Time It Takes to Administer Antibiotics to Children With Meningitis. W. L. Meadow, R. R. Tanz, P. Wallskog, D. Mendez, J. Lantos, and R. Unger. Departments of Pediatrics, Wyler Children's Hospital, University of Chicago (Ill); and Children's Memorial Hospital, Northwestern University, Chicago.
- Local Anesthesia With Lidocaine in Infant Lumbar Punctures: Effect on Infant Pain Response.
 J. R. Harley, F. K. Battan, and A. H. Novack.

- Department of Pediatrics, University of Washington and Children's Hospital and Medical Center, Seattle.
- 10:15 Rapid Screening for UTI in the Emergency Department. K. N. Shaw, D. Hexter, J. S. Schwartz, and K. McGowen. Division of General Pediatrics, Emergency Medicine, The Children's Hospital of Philadelphia (Pa).
- 10:30 Accuracy of Tympanic Thermometry in a Pediatric Emergency Department. R. Vinci, C. Garabedian, and H. Bauchner. Division of Pediatric Emergency Medicine, Department of Pediatrics, Boston (Mass) City Hospital, Boston University School of Medicine.
- 10:45 Emergency Department Pediatric Telephone Advice. D. J. Isaacman, V. Verdile, P. Kohen, and L. A. Verdile. Department of Pediatrics, Children's Hospital of Wisconsin, Milwaukee; Department of Emergency Medicine, University of Pittsburgh (Pa) School of Medicine.
- 11:00 Skull Fractures in Young Children: Do Characteristics of the Fractures Clearly Distinguish Child Abuse From Accidental Injuries? J. M. Leventhal, S. A. Thomas, N. S. Rosenfield, and R. I. Markowitz. Departments of Pediatrics and Diagnostic Imaging, Yale University School of Medicine and Yale-New Haven (Conn) Hospital.
- 11:15 Risk Factors for Neglect and Foster Care Placement in Infants of Substance Abusing Women. P. Nair, C. Kight, M. Black, P. Roby, R. Hebel, and J. Johnson. Departments of Pediatrics and Preventive Medicine, University of Maryland School of Medicine, Baltimore.
- 11:30 Sexual Abuse Characteristics Are Not Independent Predictors of Behavior Problems in Sexually Abused Children. J. E. Paradise and L. Rose. The Children's Hospital of Philadelphia (Pa); The Children's Hospital, Boston (Mass) City Hospital and Boston University School of Public Health.
- 11:45 Interobserver Evaluation of Alleged Child Sexual Abuse Victims With Focal Concave Hymenal Variations. D. L. Kerns and M. L. Ritter. Department of Pediatrics, Santa Clara Valley Medical Center, San Jose, Calif.

PREVENTION AND EPIDEMIOLOGY

Pacific B

Moderators: Fred Rivara, MD, and Ruth E. K. Stein, MD
 9:00 The Effect of Exercise and Cigarette Use During Pregnancy on Fetal Growth. H. Bauchner, L. Fried, T. Heeren, and B. Zuckerman. Departments of Pediatrics and Public Health, Boston (Mass) City Hospital/Boston University School of Medicine.

- 9:15 Incidence of Illnesses Prompting Physician Visits Among Children in Day Care. J. A. Jones, R. R. Reves, and L. K. Pickering. Departments of Community Medicine and Pediatrics, Baylor College of Medicine, and Departments of Medicine and Pediatrics, University of Texas Health Science Center at Houston.
- 9:30 Immunization Problems Identified in Hospitalized Preschool-Age Children. D. T. Casto, C. Y. J. Chan, P. R. Wood, and S. K. Jung. Departments of Pediatrics, Pharmacology, and Pharmacy, The University of Texas Health Science Center, San Antonio.
- 9:45 Home Phototherapy for Treatment of Exaggerated Neonatal Jaundice Enhances Breast-feeding. J. James, S. D. Williams, and L. M. Osborn. Department of Pediatrics, University of Utah, Salt Lake City.
- 10:00 Access to Health Care for Homeless and Other Poor Families. D. L. Wood, M. F. Shapiro, T. Hayashi, and R. B. Valdez. Department of Pediatrics, Cedars-Sinai Medical Center, the UCLA School of Medicine and the RAND Corporation, Los Angeles.
- 10:15 Advising Parents to Stop Smoking: Pediatricians' and Parents' Attitudes in Private Practice.
 B. L. Frankowski, S. O. Weaver, L. G. Morris, and R. H. Secker-Walker. Department of Pediatrics, Biometry Facility and Office of Health Promotion Research, University of Vermont, Burlington.
- 10:30 Prior Approval in a Pediatric Emergency Room. D. Glotzer, A. Sager, D. Socolar, and M. Weitzman. Department of Pediatrics, Boston (Mass) City Hospital and Boston University Schools of Medicine and Public Health.
- 10:45 Children Riding in the Back of Pickup Trucks:
 A Neglected Safety Issue. G. A. Woodward and
 R. G. Bolte. Department of Pediatric Emergency
 Medicine, Primary Children's Medical Center, University of Utah School of Medicine, Salt Lake City.
- 11:00 Barriers to Pediatric Referrals in Managed Care Systems. J. D. C. Cartland and B. K. Yudkowsky. Department of Research, American Academy of Pediatrics, Elk Grove Village, Ill.
- 11:15 Ambulance Utilization by Homeless Children.
 J. Fine, G. Foltin, M. Tunik, A. Fierman, and
 B. Dreyer. Department of Pediatrics, Bellevue
 Hospital-New York (NY) University School of Medicine.
- 11:30 Injuries in Daycare: A 5-Year Perspective on Who Incurs Them and Why. P. Fosarelli. Department of Pediatrics, The Johns Hopkins School of Medicine. Baltimore. Md.
- 11:45 Families Who Seek Care for the Common Cold in a Pediatric Emergency Room. J. H. Mayefsky, Y. El-Shinnawy, and P. Kelleher. Department of Pediatrics, Cook County Hospital, and the Chicago (Ill) Medical School.

GENERAL POSTER SESSION

Wednesday, May 9, 1990 9 ам-12:30 рм

California C

Moderators: Jay E. Berkelhamer, MD, and Thomas G. DeWitt, MD

Correlation of Maternal and Child Blood Lead Concentrations. I. Cade, C. Gosselink, E. Willis, E. Ekwo, and J. E. Berkelhamer. Department of Pediatrics, University of Chicago (Ill) Pritzker School of Medicine.

Holter Monitor and ECG Abnormalities in Children With HIV. C. A. Walsh, D. Better, H. M. Adam, B. Weiss, and C. N. Steeg. Department of Pediatrics, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY.

Compliance With Childhood Cholesterol Screening in a Health Maintenance Organization (HMO). R. P. Bachman and E. J. Schoen. Department of Pediatrics, Kaiser Permanente Medical Center, Oakland, Calif.

Medical Management of Persistent Middle Ear Effusion.
S. Berman, K. Grose, R. Nuss, C. Huber-Navin, and R. Roark. Departments of Pediatrics and Otolaryngology, University of Colorado School of Medicine and University Hospital, Denver.

Use of Clinical Observation Scales Following Antipyretic Therapy to Predict Serious Illness in Febrile Children. A. C. Richardson, K. J. Roghmann, and K. C. White. Department of Pediatrics, University of Rochester (NY) School of Medicine and Dentistry.

Temperature Relationship to Distance and Flow Rate of Warmed IV Fluids. G. Faries, C. Johnston, and R. T. Plouff. Department of Pediatrics, University of Alabama School of Medicine, Birmingham.

Highly Mobile, Previously Homeless and 'Hidden Homeless' Children: How Prevalent in a Pediatric Primary Care Setting? C. Rude and J. M. Leventhal. Department

of Pediatrics, Yale University School of Medicine, New Haven, Conn.

Physician Immunization Practices. M. Silver and L. M. Osborn. Department of Pediatrics, University of Utah School of Medicine, Salt Lake City.

Do Diabetic Children and Their Parents Talk About the Complications of the Illness? A. G. Adler, W. J. Ezekowitz, D. T. Kraemer, B. F. Sabbeth, and J. M. Leventhal. Department of Psychology, Yale University, and Department of Pediatrics, Yale University School of Medicine, New Haven, Conn.

Home Monitoring of Sickle Cell Crisis Pain. B. Shapiro, D. Dinges, L. Reilly, W. Whitehouse, E. Orne, K. Ohene-Frempong, and M. Orne. Children's Hospital of Philadelphia and Institute of Pennsylvania Hospital, University of Pennsylvania.

Pediatric Motor Vehicle Related Trauma: Patterns of Injury. P. F. Agran, D. G. Winn, and D. N. Castillo. Department of Pediatrics and Public Policy Research Organization, University of California, Irvine.

Physician Knowledge and Attitudes About Daycare. B. S. Wirth and C. L. Hausman. Department of Pediatrics, Thomas Jefferson University School of Medicine, Philadelphia, Pa.

Maternal Perception of Offspring Size Among Hispanics. I. G. Pawson, F. S. Mendoza, R. Martorell, and K. Baisden. Stanford (Calif) University, Stanford Center for Chicano Research.

Prenatal Determination of Demographic and Attitudinal Factors Regarding Breastfeeding in an Indigent Population. G. L. Freed and T. M. Jones. Department of Pediatrics, Baylor College of Medicine, Houston, Tex.

JOINT TOPIC SESSIONS

With American Pediatric Society and Society for Pediatric Research

Thursday, May 10, 1990 2 pm-5:30 pm

ADOLESCENT MEDICINE

Pacific B

Moderators: Sandra L. Elvik, MSN, CPNP,

Donald Orr, MD, and Robert Penny, MD

2:00 Oral Contraceptive Use, Serum Cholesterol, and Dietary Intake Among Adolescents. B. A. Spear,

*Abstract was published in the Program Issue of the American Pediatric Society and the Society for Pediatric Research, Pediatric Research, April 1990.

M. K. Oh, P. B. Gentry, and R. A. Feinstein. Department of Pediatrics, Division of Adolescent Medicine, University of Alabama, Birmingham.

2:15 The Course of Splenomegaly in Infectious Mononucleosis. W. A. Primos, G. L. Landry, and K. A. Scanlan. Departments of Pediatrics and Radiology, University of Wisconsin, Madison.

2:30 *Herpes Simplex Virus as a Cause of Pharyngitis
Among College Students. J. A. McMillan, L. B.
Weiner, A. P. Higgins, and V. J. Lamparella. SUNY

- Health Science Center, Department of Pediatrics, and Syracuse (NY) University Health Science Center.
- 2:45 *Attitudinal and Behavioral Concomitants of Short Stature. L. Cuttler, R. Michon, M. Reinecke, and C. Stocking. Departments of Pediatrics/ Medicine/Psychiatry, University of Chicago (Ill); Case Western Reserve University, Cleveland, Ohio.
- 3:00 Young Adolescents' Experience, Knowledge, and Attitudes About Sexual Abuse. D. Madansky, C. Edelbrock, G. Schlundt, D. Redwing, and L. Santoro. Departments of Pediatrics and Psychiatry, University of Massachusetts Medical Center and Child Assault Prevention Project, Worcester, Mass.
- *Recurrent Genitourinary Chlamydia Trachomatis (Ct) Infections in Adolescent Females.
 M. J. Blythe, B. P. Katz, B. E. Batteiger, J. A. Ganzer, and R. B. Jones. Marion County Department of Health and Indiana University School of Medicine, Indianapolis.
- 3:30 *Human Papillomavirus in Suburban Female Adolescents. M. Fisher, W. D. Rosenfeld, and R. Burk. Department of Pediatrics, North Shore University Hospital, Cornell University Medical College, Manhasset, NY; Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY.
- 3:45 *Psychosocial Correlates of Risk for STD/AIDS Among Urban High School Students. M. A. Shafer and C. B. Boyer. University of California, San Francisco, Department of Pediatrics, Division of Adolescent Medicine.
- 4:00 *Prevalence of Behaviors at High Risk for Human Immunodeficiency Virus (HIV) Transmission in Adolescents. B. Moscicki, S. Millstein, J. Broering, and C. Irwin, Jr. University of California, San Francisco, Department of Pediatrics, Division of Adolescent Medicine.
- 4:15 *Condom Use and Attitudes of Adolescent Females. C. Langefeld, B. Katz, R. Jones, M. Blythe, V. Caine, P. Dias, and D. Orr. Indiana University School of Medicine, Indianapolis.
- 4:30 Risk Factors for Suicide Attempts Among Native American Adolescents. D. C. Grossman, B. C. Milligan, and R. A. Deyo. Departments of Pediatrics and Medicine, University of Washington, Seattle; Maternal and Child Health Branch, Indian Health Service, Rockville, Md.
- 4:45 *Family Structure, Emotional Distancing and Risktaking Behavior in Adolescents. S. Forman, C. E. Irwin, Jr., R. A. Turner, and S. G. Millstein. University of California, San Francisco, Department of Pediatrics, Division of Adolescent Medicine.
- 5:00 *Parent-Adolescent Conflict and Accidental Injuries. P. E. Bijur and M. Kurzon. Albert Einstein College of Medicine, Department of Pediatrics, Bronx, NY.

**Adolescent Risk Behavior and Media Use. J. D. Klein, J. D. Brown, and K. W. Childers. University of North Carolina, School of Medicine, Clinical Scholars Program and Department of Pediatrics and the School of Journalism, Chapel Hill.

BEHAVIORAL PEDIATRICS

California A

Moderators: Barry Lester, PhD, Robert Pantell, MD, and Albert J. Solnit, MD

- 2:00 *Patterns of Interaction Among Drug Dependent Women and Their Infants. E. Fitzgerald, K. Kaltenbach, and L. Finnegan. Thomas Jefferson University, Department of Pediatrics, Philadelphia, Pa.
- 2:15 *Behavioral Patterns in Children of Mothers Using Heroin and Methadone. M. H. Lifschitz, G. S. Wilson, and G. Tortolero. Department of Pediatrics, Baylor College of Medicine, Houston, Tex.
- 2:30 *Very Low Birthweight (VLBW) Children at 8
 Years of Age: Sex Specific Effects on IQ, Behavior and Academic Achievement. N. Breslau,
 M. Hack, D. Aram, N. Klein, B. Weissman, and
 E. Borowski. Case Western Reserve University,
 Cleveland, Ohio.
- 2:45 *Extremely Low Birthweight Preemies and Their Peers: A Comparison of Preschool Performance.
 C. L. Halsey, M. F. Collin, and C. L. Anderson. Loyola University Medical Center, Department of Pediatrics, Maywood, Ill; MetroHealth Medical Center, Department of Pediatrics, Cleveland, Ohio.
- 3:00 *Enhancing the Home Environment of Low Birth
 Weight, Premature Infants. P. H. Casey,
 R. H. Bradley, B. M. Caldwell and R. T. Gross.
 Infant Health and Development Program, UAMS/
 ACH-Dennis Dev Center, Little Rock, Ark.
- 3:15 *Maternal Behavioral Intervention (MBI) with Mothers of Full-Term (FT) Intrauterine Growth Retarded Infants (IUGR) Accelerates Postnatal Growth During the Neonatal Period. C. G. Coll, L. F. Halpern, B. M. Lester, B. R. Vohr, and W. Oh. Brown University, Women & Infants' Hospital, Department of Pediatrics, Providence, RI.
- 3:30 *Children of Battered Women: Developmental Profiles. S. R. Wildin, W. D. Williamson, and G. S. Wilson. Baylor College of Medicine, Texas Children's Hospital, Department of Pediatrics, Houston, Tex.
- 3:45 *Aberrant Behaviors of Young Boys with Fragile X Syndrome, A. M. Lachiewicz, G. A. Spiridi-

^{*}Abstract was published in the Program Issue of the American Pediatric Society and the Society for Pediatric Research, Pediatric Research, April 1990.

- gliozzi, C. A. Gullion, and S. K. Ransford. Duke University Medical Center, Department of Pediatrics, Durham, NC; Southwestern Medical Center, Department of Psychiatry, Dallas, Tex.
- 4:00 Hearing Loss and Attention Deficits: Etiological Considerations. D. Kelly, B. Kelly, M. Jones, N. Moulton, S. Verhulst, and S. Bell. Department of Pediatrics, Southern Illinois University School of Medicine, Springfield, and Illinois School for the Deaf, Jacksonville.
- 4:15 *Adverse Side Effects of Methylphenidate (MPH)
 Among Mentally Retarded (MR) Children With
 Attention Deficit Hyperactivity Disorder
 (ADHD). B. L. Handen, H. Feldman,
 A. Gosling, and A. M. Breaux. University of
 Pittsburgh (Pa), Children's Hospital of Pittsburgh,
 Department of Pediatrics.
- 4:30 Phobias Following Child Sexual Abuse. B. S. Wirth and A. R. DeJong. Department of Pediatrics, Jefferson Medical College of Thomas Jefferson University, Philadelphia, Pa.
- 4:45 Stress and Adjustment in Boys with Hemophilia.

 J. M. Perrin, W. E. MacLean, R. L. Janco, and S. L. Gortmaker. Children's Service, Massachusetts General Hospital, and Harvard University Medical School and School of Public Health, Boston; Vanderbilt University School of Medicine, Nashville, Tenn.
- 5:00 Identification and Management of Psychosocial Problems in Pediatric Primary Care. S. M. Horwitz, P. J. Leaf, J. M. Leventhal, B. W. C. Forsyth, and K. N. Speechley. Departments of Epidemiology and Public Health and Pediatrics, Yale University, New Haven, Conn.
- 5:15 Factors Influencing Frequent Pediatric Emergency Room Use. C. Gosselink, D. Brazdziunas, A. Saulys, M. Lehmann, A. Kresheck, E. Ekwo. La Rabida Children's Hospital and Research Center, Department of Pediatrics, University of Chicago (III).

EPIDEMIOLOGY AND PREVENTIVE PEDIATRICS

California B

Moderators: Mark Klebanoff, MD, Eugene Shapiro, MD, and Myron E. Wegman, MD

- 2:00 *Factors Affecting Compliance With Newborn Follow-Up. J. R. Harty, M. A. Rapoff, K. L. Wible, and J. G. Hollowell. University of Kansas Medical Center, Department of Pediatrics, Kansas City.
- 2:15 *Accuracy of Perinatal Hospital Discharge Infor-
- *Abstract was published in the Program Issue of the American Pediatric Society and the Society for Pediatric Research, Pediatric Research, April 1990.

- mation. R. W. Armstrong, G. C. Robinson, M. R. Pendray, S. B. Effer. University of British Columbia, Sunny Hill Hospital for Children, British Columbia's Children's Hospital and Grace Hospital, Vancouver, Canada.
- 2:30 *Lead Exposure, Otitis Media, and Central Auditory Processing in Inner-City Children. O. G. Berger, K. N. Dietrich, and R. Keith. Departments of Pediatrics, Environmental Health and Otolaryngology, University of Cincinnati (Ohio).
- 2:45 *Perinatal Exposure to Polychlorinated Biphenyls (PCB's) and Child Development at 18 & 24 Months. W. J. Rogan and B. C. Gladen. NIEHS, Research Triangle Park, NC.
- 3:00 *Epidemiologic Studies on the Health Hazards of Child Labor. P. J. Landrigan, S. Pollack, R. Belville, and R. McConnell. Division of Occupational and Environmental Medicine, Mount Sinai Hospital, New York, NY.
- 3:15 Unsuspected Cocaine Exposure in Young Children. S. Kharasch, R. Vinci, D. Glotzer, J. Sargent, and M. Weitzman. Department of Pediatrics, Division of Emergency Room Services, Boston (Mass) City Hospital, Boston University School of Medicine.
- 3:30 Factors Associated With Delay in Diagnosis of Childhood Amblyopia. L. R. Campbell and E. Charney. Department of Pediatrics, Sinai Hospital and The Johns Hopkins University, Baltimore, Md.
- 3:45 Hemoglobin Norms for Minority Inner City Infants. M. Irigoyen, L. L. Davidson, and C. Seaman. Department of Pediatrics, Columbia University and Babies Hospital, New York, NY.
- 4:00 Socioeconomic Status (SES) and Survival in Childhood Acute Lymphoblastic Leukemia (ALL). G. Dougherty and M. S. Kramer. Departments of Pediatrics and Epidemiology and Biostatistics, McGill University Faculty of Medicine, Montreal, Canada.
- 4:15 *Reduced Transplacental Measles Antibody
 Transfer in a Well Vaccinated Society. L. Chui,
 R. Marusyk, D. Harbora, and H. F. Pabst. Department of Medical Microbiology and Infectious
 Diseases and Department of Pediatrics, Faculty of Medicine, University of Alberta, Edmonton, Canada.
- 4:30 *Evaluation of Hepatitis B Prophylaxis in a Large Municipal Hospital. J. M. Birnbaum and K. Bromberg. SUNY Health Science Center at Brooklyn (NY), Kings County Hospital, Department of Pediatrics.
- 4:45 *Practices of Primary Care Physicians in Initiating Diphtheria, Tetanus and Pertussis (DTP)
 Immunizations in Prematurely Born Children.
 D. L. Langkamp. University of Wisconsin, Department of Pediatrics, Madison.
- 5:00 *Prolonged Asymptomatic Giardia Lamblia Infection in Day-Care Children. S. H. Korman,

- N. Strauss, M. Ish-Horowicz, A. HaLevy, U. Har-Even, and R. J. Deckelbaum. Hadassah University Hospital, Departments of Pediatrics and Biostatistics, Jerusalem, Israel, and Columbia University, Department of Pediatrics, New York, NY.
- 5:15 *The Preexisting 'Normality' of SIDS Victims. J. A. Taylor, J. E. Haas, and A. B. Bergman. Children's Hospital Medical Center and the University of Washington, Seattle.

GENERAL PEDIATRICS

Pacific A

Moderators: William Cleveland, MD, Thomas DeWitt, MD, and John Leventhal, MD

- 2:00 Black Clouds: So Some Residents Really Work Harder? R. R. Tanz and J. Charrow. Department of Pediatrics, Northwestern University Medical School and Children's Memorial Hospital, Chicago, Ill.
- 2:15 *Morbidity and Outcome of Pregnancy in Resident Physicians as Compared to Other Professional Working Women. A. N. Plumb, P. S. Simmons, S. R. Wynn, P. C. O'Brien, J. E. Brazy, and K. L. Noller. Mayo Medical School and Mayo Clinic, Rochester, Minn, University of Wisconsin, Madison.
- 2:30 *A Study of Psychological Response to the Demands of Call Duty in Pediatric Residents.

 W. Rusin and K. Berkoff. Rainbow Babies & Children's Hospital and Case Western Reserve University, Cleveland, Ohio.
- 2:45 *Higher Blood Pressures Associated with On-Call Stress as Measured With an Ambulatory Blood Pressure Monitor (ABPM). R. J. Yetman, M. S. West, and R. J. Portman. University of Texas Medical School-Pediatrics, Houston.
- 3:00 Predicting Students' Exam Results From Their Pediatric Clerkship Performance. L. W. Greenberg and P. Getson. Children's National Medical Center, and Department of Pediatrics, The George Washington University School of Medicine, Washington, DC.

- 3:15 *Poor Correlation Between Third-Year Medical Student Pediatric NBME Scores and Performance in Clinical Clerkship. R. L. Janco and M. L. Summar. Vanderbilt University School of Medicine, Department of Pediatrics, Nashville, Tenn.
- 3:30 Effectiveness of Computer Generated Appointment Reminders. T. G. Quattlebaum, P. M. Darden, and J. B. Sperry. Department of Pediatrics, Medical University of South Carolina, Charleston.
- 3:45 *Non-Compliance (N-C) in Renal Allograft Recipients (R) in the 1980's. B. M. Korsch, V. Negrete, J. Marek, R. B. Ettenger, and R. N. Fine. UCLA School of Medicine, University of Southern California School of Medicine & CHLA, Los Angeles.
- 4:00 *'User Friendly' Computerized Quality Assurance Program for Regionalized Neonatal Care.
 S. M. Donn and M. R. Gates. University of Michigan Medical Center, Departments of Pediatrics and Nursing, Ann Arbor.
- 4:15 *Timing of Initial Tympanostomy-Tube Placement in Infants With Cleft Palate. J. L. Paradise and B. A. Elster. University of Pittsburgh (Pa), Cleft Palate Center and School of Medicine, Department of Pediatrics.
- 4:30 Abdominal X-rays, Intussusception and the E.D.
 D. Smith, C. Walsh-Kelly, H. Hennes,
 M. Melzer-Lange, W. Bonadio, J. Losek, and
 P. Glaeser. Department of Pediatrics, Medical College of Wisconsin, and Children's Hospital of Wisconsin, Milwaukee.
- 4:45 Cost Effectiveness of Erythromycin Versus Mupirocin for the Treatment of Impetigo in Children. T. D. Rice, A. K. Duggan, and C. DeAngelis. Department of Pediatrics, The Johns Hopkins Medical Institutions, Baltimore, Md.
- 5:00 *Evaluation of the Technicon H-1 (H-1) Hematology Analyzer for Identification of Occult Bacteremia (OB) in Children. A. F. Rodriguez, S. L. Kaplan, M. V. Gresik, and E. O. Mason, Jr. Baylor College of Medicine, Texas Children's Hospital, Departments of Pediatrics and Pathology, Houston.
- 5:15 *Clinical vs. Roentgenographic Assessment of Adenoidal Obstruction in 870 Children. J. L. Paradise, B. S. Bernard, and D. K. Colborn. University of Pittsburgh (Pa), School of Medicine, Department of Pediatrics, Children's Hospital of Pittsburgh.

^{*}Abstract was published in the Program Issue of the American Pediatric Society and the Society for Pediatric Research, Pediatric Research, April 1990

GENERAL PLENARY SESSION

Friday, May 11, 1990 8:15 AM-Noon

Pacific A

Moderator: Carol Berkowitz, MD

- 8:15 Cost Analysis of a Pre-Paid, Capitated, Managed-Care Program for Medicaid Children. T. D. Sullivan. Department of Pediatrics, SUNY at Buffalo (NY), School of Medicine, The Children's Hospital of Buffalo.
- 8:30 Readability of Childhood Immunization Consent Forms. S. T. Melman, J. M. Kaplan, M. L. Caloustian, J. Smith, and J. A. Weinberger. Department of Pediatrics, Hahnemann University Hospital and Center for Literacy. Philadelphia, Pa.
- 8:45 Efficacy of Nebulized Metaproterenol in Improving Symptoms of Children With RSV Bronchiolitis. A. J. Alario, W. Lewander, P. Dennehy, R. Seifer, and A. Mansell. Department of Pediatrics, Brown University, Providence, RI.
- 9:00 The Risks and Benefits of Acetaminophen Antipyresis in Young Children With Fever of Presumed Viral Origin. M. S. Kramer, L. E. Naimark, R. Roberts-Brauer, A. McDougall, and D. G. Leduc. Departments of Pediatrics and Epidemiology and Biostatistics, McGill University, Montreal, Canada.
- 9:15 Lower Respiratory Illness in Infants and Low Socioeconomic Status. P. A. Margolis, R. Greenberg, and The Infant Health Study Group. Department of Pediatrics, University of North Carolina, Chapel Hill.
- 9:30 PRESIDENT'S ADDRESS
- 10:00 INTERMISSION
- 10:15 Do Retinal Hemorrhages Occur With Accidental Head Trauma in Young Children? A. Alario, A. Duhaime, W. Lewander, W. Tsiaras, M. Wallach, and J. S. O'Shea. Departments of Pediatrics, Ophthalmology, and Radiology, Brown University, Providence, RI; Department of Neurosurgery, University of Pennsylvania, Philadelphia.

- 10:30 Unscheduled Return Visits to a Pediatric Emergency Department: A Prospective Study. M. Letourneau, D. Jaffe, D. Hodge, III, and E. Zieserl. Department of Pediatrics, Children's Memorial Hospital, Chicago, Ill.
- 10:45 The Denver II: Revision and Restandardization of the DDST. W. Frankenburg, J. Dodds, P. Archer, B. Bresnick, and H. Shapiro. Departments of Pediatrics and Preventive Medicine, University of Colorado, School of Medicine, Denver.
- 11:00 Endotracheal Tube Selection in Children: A Comparison of Four Methods. B. R. King, M. D. Baker, M. S. Schreiner, and J. V. DiCarlo. The Divisions of General Pediatrics, Emergency Medicine, and Anesthesia and Critical Care Medicine, The Children's Hospital of Philadelphia (Pa).
- 11:15 Is a Chest X-ray Necessary in the Evaluation of Every Febrile Infant Less Than Eight Weeks of Age? D. Bulis, E. Crain, H. Goldman, and P. Bijur. Departments of Pediatrics and Radiology, Albert Einstein College of Medicine, Division of Ambulatory Care, Bronx (NY) Municipal Hospital Center.
- 11:30 Use of Randomized Response to Estimate Substance Use in a School-Based Clinic Population.

 M. Fisher, L. Kupferman, and M. Lesser. Departments of Pediatrics and Research, North Shore University Hospital-Cornell University Medical College, Manhasset, NY; New York (NY) City Department of Health.
- 11:45 What Happens After Preschool Vision Screening in Pediatric Practice? R. C. Wasserman, S. E. Brotherton, and C. A. Croft. Pediatric Research in Office Settings (PROS) Network, American Academy of Pediatrics (AAP), Elk Grove Village, Ill.

SCHEDULE OF EVENTS-1990 ANNUAL MEETING

THE AMERICAN PEDIATRIC SOCIETY AND

THE SOCIETY FOR PEDIATRIC RESEARCH

Anaheim Hilton and Convention Center

Monday, May 7	Tuesday, May 8	Wednesday, May 9	Thursday, May 10
	8 AM-9 AM APS Plenary Session APS Presidential Address St Geme Award	8 AM-9:30 AM SPR Plenary Session SPR Presidential Address Young Investigator Award	8 am-11:30 am Subspecialty Platform Sessions III
	9 AM-12:30 PM APS Presidential Symposia and concurrently Subspecialty Platform Sessions I	Rowe Award House Officer & Medical Student Research Awards 9:30 AM-Noon Poster Symposia (Convention Center— Pacific Room)	11:30 am-1 pm SPR Business Meeting
	12:30 PM-2 PM APS Business Meeting 12:30 PM-6 PM	9:30 am-2:30 pm Poster Session III* Commercial Exhibits (Convention Center— Southwest Hall)	
	Poster Session II* Commercial Exhibits (Convention Center— Southwest Hall)		·
2.20 m. 6 m.	2 pm-3 pm APS Howland Award 3:30 pm-6 pm Poster Symposia (Convention Center— Pacific Room)	1:30 pm-5 pm Subspecialty Platform Sessions II	2 pm-5:30 pm SPR Presidential Symposia and concurrently Subspecialty Platform Sessions IV
3:30 pm-6 pm Poster Symposia (Convention Center— Pacific Room) 3:30 pm-7:30 pm Poster Session I* Commercial Exhibits (Convention Center— Southwest Hall)			*Posters will be unattended for a portion of this time. Please check poster session schedule for author attendance times.

THE AMERICAN PEDIATRIC SOCIETY AND THE SOCIETY FOR PEDIATRIC RESEARCH SUBSPECIALTY PLATFORM SCHEDULE - 1990

descions i
Tuesday, May 8 9 am-12:30 pm

GEOGRANIC I

Critical Care I (Laguna AB)

Developmental Pharmacology I (Palos Verdes)

Endocrinology I (Pacific A)

Genetics I (Huntington ABC)

Immunology I (California A)

Neonatal Epidemiology and Follow-up I

(California D) Neonatal Infectious Diseases I (Pacific B)

Neonatal Nutrition & Metabolism (California B)

Neonatal Pulmonology I (California C)

SESSIONS II Wednesday, May 9 1:30 рм-5 рм

Cardiology I (California A)

Developmental Biology I (Huntington ABC)

Developmental Pharmacology II Developmental Biology II (Laguna AB)

Dysmorphology & Teratology (Palos Verdes AB)

Gastroenterology/Nutrition I (California D)

Hematology and Oncology I (California B)

Immunology II (California C)

Metabolism & Diabetes I (Pacific A)

Neonatology-General I (Pacific C)

Nephrology I (Pacific B)

Pulmonology I (Pacific D)

SESSIONS III Thursday, May 10 8 AM-11:30 AM

Cardiology II (California B)

Clinical Bioethics (Palos Verdes AB)

(Huntington ABC)

Endocrinology II (California C)

Genetics II (Pacific B)

Hematology and Oncology II (Laguna AB)

Infectious Diseases I (Pacific D)

Neonatology-General II (Pacific C)

Nephrology II (California A)

(California D)

Neurology I (Pacific A) Pulmonology II

SESSIONS IV Thursday, May 10 2 рм-5:30 рм

Adolescent Medicine (Pacific B)

Behavioral Pediatrics (California A)

Epidemiology & Preventive Pediatrics

(California B)

Gastroenterology/Nutrition II (California C)

General Pediatrics & Pediatric

Education (Pacific A)

Infectious Diseases II (Pacific D)

Metabolism & Diabetes II (Laguna AB)

Neonatal Cardiology (Huntington ABC)

Neonatal Immunology/Hematology (California D)

1990 APS/SPR/APA CONFIRMED EXHIBITORS

Booth No(s). **Company Name** City, State Airborne Life Support Systems Houston, Tex 233A, 233, 132 Air-Shields Vickers, A Vickers PLC Co Hatboro, Pa Alpha Therapeutic Corporation Los Angeles, Calif 424 Washington, DC 209 American Red Cross 124, 126 Baxter Hyland Division Glendale, Calif Riverside, Calif 203 Bear Medical Systems Inc Bristol, Tenn 513, 515, 302 Beecham Laboratories Bunnell Incorporated Salt Lake City, Utah 533, 432 Burroughs Wellcome Company 230, 231A Research Triangle Park, NC 333, 232 Ft. Lauderdale, Fla CarePlus Los Angeles, Calif 507, 509 Carnation Nutritional Products Lakewood, Colo 426 COBE Laboratories Inc 213 Cook Critical Care Bloomington, Ind Corometrics Medical Systems Wallingford, Conn 102 225 Montvale, NJ Datascope Cranston, RI 201 Davol Inc Indianapolis, Ind Eli Lilly and Company 519, 521 Springfield, Ill 313, 315 EM-SCAN Inc Chicago, Ill 220 Encyclopaedia Britannica Inc 300 Tarzana, Calif **Endocrine Sciences** 418 Fiberoptic Medical Products Inc Allentown, Pa

Company Name	City, State	Booth No(s).
Genentech Inc	So. San Francisco, Calif	319, 321
Gerber Products Company	Fremont, Mich	218
Hemocue Inc	Laguna Hills, Calif	100
Herbert Laboratories	Santa Ana, Calif	224
Hewlett-Packard Company	Waltham, Mass	433, 332
ICN Pharmaceuticals Inc	Costa Mesa, Calif	219, 221
Infrasonics Inc	San Diego, Calif	212
J. B. Lippincott Company	Philadelphia, Pa	118
La Leche League International Inc	Franklin Park, Ill	231A
Lea & Febiger	Philadelphia, Pa	108
Loma Linda Foods	Riverside, Calif	407
Marquette Electronics	Milwaukee, Wis	425
Mead Johnson Nutritionals	Evansville, Ind	206, 208
Medcomp	Harleysville, Pa	214
Med-Science	Needham Heights, Mass	412
Medfusion Inc	Duluth, Ga	309
Medical Associated Services	Hatfield, Pa	400
Medical Data Systems	Wayne, Pa	114
Medical Research Center	New York, NY	324
Mosby-Year Book Inc	St. Louis, Mo	409
Natus Medical Inc	Foster City, Calif	503
N.I.C.H.D.	Bethesda, Md	215
Nihon Kohden America Inc.	Irvine, Calif	427
Nova Metrix Medical Systems Inc	Wallingford, Conn	431, 330
Ohmeda	Madison, Wis	525, 527
Palco Laboratories	Santa Cruz, Calif	226
Promedica Inc	Burlingame, Calif	501
Rorer Pharmaceuticals	Fort Washington, Pa	130, 231
Ross Laboratories	Columbus, Ohio	200, 202
Sandoz Pharmaceutical	East Hanover, NJ	401, 403
SensorMedics Corporation	Anaheim, Calif	306, 308
Serono Laboratories Inc	Norwell, Calif	327
SpaceLabs Inc	Redmond, Wash	325
Specialty Laboratories Inc	Santa Monica, Calif	402
Springer-Verlag New York Inc	New York, NY	414
Transonic Systems Inc	Ithaca, NÝ	531
U.S. Navy Recruiting	Los Angeles, Calif	326
Vygon Corporation	E. Rutherford, NJ	303
W. B. Saunders	Philadelphia, Ýa	207
Williams & Wilkins	Baltimore, Md	301
Wyeth-Ayerst Laboratories Inc	Philadelphia, Pa	112, 120

1990 APS/SPR/APA EXHIBITS SCHEDULE

Southwest Exhibit Hall, Convention Center, Anaheim, Calif, May 7-9

Monday, May 7, 3:30 рм-7:30 рм, Wine Reception in Lounge Area

Tuesday, May 8, 12:30 рм-6 рм Complimentary Drinks Wednesday, May 9, 9:30 дм-2:30 рм Complimentary Drinks

Abstracts

Annual Meeting of the Ambulatory Pediatric Association

ADOLESCENT MEDICINE AND PEDIATRIC EDUCATION

Urinary Leukocyte Esterase Screening for Asymptomatic Sexually Transmitted Disease in Adolescent Males

M. J. Werner and F. M. Biro

Division of Adolescent Medicine, Children's Hospital Medical Center, Cincinnati, Ohio

Appropriate screening methods for sexually transmitted disease in asymptomatic adolescent males continue to be an issue. Several reports have supported the use of the dipstick for urinary leukocyte esterase on first-catch urine specimens; however, proper specimen collection can be difficult to obtain. The ability of the urinary leukocyte esterase test on a random urine specimen to predict Chlamydia trachomatis and Neisseria gonorrhoeae (GC) urethritis among asymptomatic adolescent males was evaluated. Sixty-eight sexually active males ages 16-21 provided urine samples for esterase screening as part of an ongoing study; 13 (19%) tested positive. Urethral cultures for GC and Chlamydia were obtained from all patients within 5 days of the urinalysis. Chlamydia was isolated from 6 (9%) and GC from 4 (6%). The sensitivity was 78%, specificity 90%, positive predictive value 54%, and negative predictive value 96% for the esterase test, when compared to positive cultures for either GC or Chlamydia. This screening method meets the critical criterion of having a high negative predictive value for asymptomatic Chlamydia or GC infections (i.e., identified almost all infected patients). These results closely approximate those obtained using first-catch urine. Using an esterase level ≥ trace as positive gave the best combination of sensitivity and specificity. Excluding Chlamydia-positive subjects, when evaluating for asymptomatic GC alone (N = 76, infected = 5)the sensitivity increased to 100% and specificity to 92%. These results support the use of the urinary leukocyte esterase test as a noninvasive and cost-effective screening method which may be used on random urine specimens to detect urethritis among adolescent males.

Intergenerational Transmission of School-Age Parenthood

S. M. Horwitz, L. V. Klerman, H. S. Kuo, and J. F. Jekel Departments of Epidemiology and Public Health, Yale University, New Haven, Conn

Previous research suggests that adolescents born to young mothers are more likely to become young parents when compared to adolescents born to older mothers. Little is known, however, about the rate and predictors of school-age parenthood in cohorts of offspring born to school-age mothers. We examined the rate and predictors of school-age parenthood in offspring born to 154 young (13-18 yr.), black, primiparas enrolled in an early (1967-1969) program for school-age mothers. We located 128 of 149 living women ($\frac{28}{0}$) and interviewed 121 (95%). Of the adolescents born to these women, 2 could not be interviewed, 2 refused, 6 were not located, and 111 were interviewed (92%).

Of these 111 adolescents, mean age was 18, 42% were female, 83% had completed or were in high school, 62% lived with their mothers, and 74% were employed. Four females (8.5%) and 1 male (1.6%) met DSM-III criteria for depression. Seven males (6.3%) met criteria for alcohol abuse. Ninety-four percent of these adolescents were sexually active, 56 (50%) reported beginning sex before age 14, and 41% reported always using birth control. Forty-two percent had been pregnant or impregnated someone and 12.6% (9 females—19%; 5 males—8%) had a child at ≤18 years.

Predictors of school-age parenthood in these adolescents included 4 factors related to the offspring's own mother and his/her early environment: maternal depression (RR = 3.3); maternal 20-year educational/economic failure (RR = 2.1); having a mother who was pregnant within two years of his/her birth (RR = 2.0); and living with just his/her mother at 2 years of age (RR = 2.5). Schoolage parenthood was also associated with adolescent features: depression (RR = 3.3), being female (RR = 2.5), low self-esteem (RR = 2.4), and absence of a confidant (RR = 3.5).

We conclude that adolescent offspring born to school-age mothers do not uniformly become school-age parents themselves. Rather, adolescents were at high risk to become young parents if their mothers were depressed, long-term educational/economic failures, and had a second pregnancy and were living alone within 2 years of their births.

The Effects of Prenatal Social Support on Infant Birthweight and Parturition for Nulliparous Teen Mothers: A Prospective Study

J. M. Pascoe

Department of Pediatrics, University of Wisconsin, Madison

PURPGSE: To examine the association between prenatal social support and the dependent variables duration of labor and infant birthweight in a sample of nulliparous teen mothers.

METHOD: Thirty consecutive nulliparous indigent teen mothers who were referred to a community-based birth companion project were studied. Eight dropped out before delivery. Data on twenty two mothers were compiled during a third trimester home

visit by a trained nurse. Several psychosocial factors were assessed including maternal social support (Maternal Social Support Index-MSSI) and depression (Center for Epidemiologic Studies Depression Scale). Mothers' and infants' hospital charts were reviewed. Data analysis was performed using the Statistical Analysis System. Test statistics included unpaired t-test, analysis of covariance

and stepwise regression.

EESULTS: Significant associations were noted between third trimester social support, duration of labor and infant birthweight. Prenatal social support explained a significant amount of variance (EV=16%, p=0.03) after amniotomy, labor induction and support during labor were included (total EV=50%). In addition, mothers with MSSI scores below the sample median delivered smaller infants (3066 \pm 109 GMS) compared to others with higher levels of support (3526 \pm 105 GMS, p=0.01). Prenatal social support remained a significant predictor of infant birthweight after controlling for weight gain and gestational age. Maternal depression was significantly and inversely associated with infant birthweight.

CONCLUSIONS: Higher levels of prenatal social support for nulliparous teen mothers are associated with shorter labors and the delivery of larger infants. Subsequent research should prospectively study possible biological mediators including prenatal nutrition and serum epinephrine levels during parturition.

Does Acne Affect Adolescents' Self-Concept?

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Although acne is believed to affect adolescents' self-concept adversely, this hypothesis has not been empirically studied. To describe the self-concept of adolescents with acne and to determine if their self-concept is affected by medical treatment, we evaluated 39 adolescents presenting for care to a community-based dermatologist. Prior to and following treatment, subjects completed a self-assessment questionnaire, the Piers-Harris Self-Concept Scale, and underwent an objective assessment of acne severity using an established five-point scale.

The mean age of subjects was 15.6 yrs., 67% were males, and all were white. Acne was rated by the dermatologist to be mild in 28% of subjects, moderate in 41%, severe in 28%, and very severe in 3%. As a result of their acne, 58% of subjects were displeased with their facial appearance, 75% were embarrassed, and 53% felt socially inhibited. Embarrassment attributed to acne was significantly correlated with social inhibition (r=.51, p=.001). Females reported greater embarrassment due to acne than males (Mann-Whitney U=80, p=.007). Despite these findings, the mean Perharris Tctal Raw Score (PHTRS) for the study group (59.7 ± 9.7) was within the expected normal range. PHTRS was not significantly correlated with acne severity or the other variables described above.

Fourteen subjects (36%) returned for follow-up a mean of 5.4 months after beginning treatment. Acne severity improved significantly as rated by the dermatologist (z=-2.80, p=.005) and subjects (z=-2.80, p=.005, Wilcoxon Matched-Pairs Signed-Ranks Test). Subjects also reported enhanced peer approval of facial appearance (z=-2.02, p=.043), a reduction in embarrassment (z=-2.20, p=.028), and decreased social inhibition (z=-2.36, p=.018). In addition, there was a statistically significant improvement in mean PHTRS (59.0±8.5 to 62.4±7.1, p=.011, paired t-test).

Our data demonstrate that acne has a tangible impact on adolescents, causing discomfort with facial appearance, embarrassment, and social inhibition. While subjects' self-concept scores were within the normal range, our study suggests that successful treatment of acne may be associated with improved self-concept.

The Effect of a Weight Management Program on Self Esteem and Body Image in Obese Youth

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Obese children and adolescents often experience social prejudice and discrimination and are at risk for low self-esteem and poor body image. This study was attempted to determine the effect of a 3 month behavioral modification weight management program, Shapedown, on improving body image and self esteem in obese children and adolescents. Data were analyzed from 21 children, aged 6-11 yrs, (70% girls) and 22 adolescents, aged 12-18 yrs (77% girls) who completed separate programs. Anthropometric measurements, the Harters' Self Perception Profile and a pictorial body image questionnaire, were completed pre and post intervention. Overall, there was no change in the weight or % ideal body weight (%IBW) for children (pre=71kg, 180%IBW; post=71kg, 178% IBW) or adolescents (pre & post = 95kg; 171% IBW). All were dissatisfied with their bodies and displayed no significant change in their perceptions of their current or ideal body shape. However, after the intervention children showed significant improvements in perceived competence for social acceptance (p = .016) and physical appearance (p = .014); while adolescents had higher scores for social acceptance (p = .004), physical appearance (p = .004), romance (p<.001), and self worth (p=.037). To determine the effect of weight, %IBW was used to identify 3 weight classes (≤150% IBW, >150% ≤200% IBW, >200% IBW). For teens, only those ≤150% IBW perceived their final body shape to be thinner (p=.009). This group showed significant improvement in social (p=.05), physical appearance (p=.02), romance (p=.009), and self-worth (p=.06). Those >150 ≤200% IBW improved in romance (p=.07). Scores for children >150 ≤200% IBW improved in social (p=.016), physical appearance (p=.05), and self-worth (p=.02). Those >200% IBW showed no improvement. In conclusion, although we saw no impact on weight loss, the program had a significant effect on self esteem for certain weight classes of children and adolescents.

Chlamydia Cervical Infection in Adolescents: A Prospective Longitudinal Follow-up

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In order to define an acceptable frequency for chlamydia (CT) screening in sexually active adolescents, we determined the incidence of new and repeat infection in a cohort of 152 girls followed from 6 to 44 months, with at least 2 STD screening examinations. Tissue culture method was used for isolation of CT. Each CT-positive patient (pt) was treated, counseled for treatment of partners, and asked to return 3-4 wks after completion of treatment for a test of cure (TOC) evaluation. In addition, all pts were to return q 4-mon for routine family planning services. Mean follow-up period was 17.3 ± 8.0 mon and 152 pts had 462 exams during the study period of 44 mon. 91% were black. Mean age was 16.6 ± 1.4 yrs, age at first sex 14.0 ± 1.9 , duration of sexual activity 2.6±1.4 yrs, number of lifetime partners 3.0±2.3, and duration of oral contraceptive (OC) use 19.7 ± 12.6 mon. 63% had 1 or more new partners during the study period. During their last visit to the clinic, reported condom use rate in the immediate past 4 months was "never" in 32.0%, "sometimes" in 47.4% and "always" in 20.6%.

Cumulative CT-pos rate was 37.5% (57/152); 23.0% (35/152) were CT-pos on initial screening. Follow-up (FU) test of those with CT-pos was also pos in 8/57 (14%). Among 49/57 (86%) who had negative FU test, in 7 "reinfection" occurred during the study

period. Overall, 15/152 (9.9%) had repeat CT-pos, 42/152 (27.6%) single CT-pos and 95/152 (62.5%) remained CT-neg during the study period. No significant difference was found between CT-neg and CT-single groups in demographic/behavioral variables. Compared with CT-neg, CT-repeat group had been on OCs longer (25 \pm 14 mon vs 16 \pm 12 mon; p=.05), had the lowest rate of consistent condom use (7.7% vs 20.4% in CT-neg; RR=3.9) and all 15/15 CT-repeat group had acquired new partners during the study. FU period was the longest among CT-repeat group (21.5 \pm 8 mon vs 16.0 \pm 8 mon in CT-neg, p<.01; 19.0 \pm 9 mon in CT-single).

We conclude that: (1) An alarmingly large number of sexually active teenagers contract CT infection within first few years of sexual activity, (2) An annual CT screening is not sufficient in this population, and (3) A subset of this population has health care

needs that are far more demanding than others.

Pediatrician's Choices to Work Full-Time (FT) or Part-Time (PT)

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In 1989, women made up 60% of the entering pediatric internship group. To assess how this shift toward female practitioners might affect future practice patterns in pediatrics, we surveyed 250 female and 125 male pediatricians chosen at random from the American Academy of Pediatrics 1988-1989 Directory about their decisions to work FT or PT. Of this group, 162 (111 women and 51 men) responded after a first mailing, a 50% response from those who were currently in active practice.

The average age for women was 39.4 y which was not significantly different between FT and PT women (39.7 vs. 38.4). The men's average age was 46 y. Five of 51 (10%) men and 27/111 (25%) women work PT (p<0.03); 19/84 (23%) FT women and 2/46 (4%) FT men had worked PT in the past (p<0.006). Reasons for working PT varied. 22 (78%) PT women listed family obligations as a primary reason; of the 5 PT men, 3 were semi-retired, 1 was in law school, and 1 was sharing child-care duties. 19/48 (39%) women with children under 6 were working PT. 29/85 (34%) FT women had no children compared to 1/26 (4%) PT women (p=0.005); 5/45FT men and 0/5 PT men have no children (NS). FT women felt they did 66% of the childcare compared to their spouses, while PT women averaged 80% and FT men 20% of child care. 21 PT women (74%) said they were paid proportionally to their FT colleagues. Although 14 PT women (52%) felt that working PT compromised their careers, all were either happy with their schedules or wished to work less. 14 (54%) PT women expected to continue PT work, while 51 (61%) FT women and 20 (43%) FT men said they would rather be working PT. 24/35 (69%) FT women in academic positions did research; 1 of 8 (12%) PT academic women did research (p = 0.005)

Conclusions: 1) 25-50% of women pediatricians work part-time at some point in their careers. 2) as more women enter pediatrics, and decisions to work PT become more common, health manpower needs in pediatrics may need to be re-evaluated.

Fitness, Body Fat and Perceived Stress in Residents

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We analyzed components of cardiovascular health, fitness, and perceived stress in nine males and nine females before and after

the first year of pediatric or family medicine residency. Measurements included standard anthropometry, percent body fat (hydrostatic weighing), maximal oxygen consumption (VO₂ max), physical activity patterns (7-day recall; motion sensor counts/awake hour), 7-day food records, blood pressure (BP), lipid profiles, and perceived stress (Osipow-Spokane scales). All eligible men and 56% of eligible women participated; mean age was 26.8 ± 3.0 years.

In men, the percent body fat increased from $18.04\pm3.95\%$ to $19.96\pm3.75\%$ (p<0.01) and lean weight fell from 62.1 ± 5.6 to 60.8 ± 5.5 kg (p<0.05); total weight was unchanged. The sum of 12 skinfolds rose 23% (p<0.001). VO₂ max fell from 54.6 ± 6.0 to 52.5 ± 5.6 ml/min/kg (p<0.05). None of these changed in the women, whose initial percent body fat was $26.7\pm3.7\%$, lean weight

 44.4 ± 3.8 kg, and VO₂ max 46.4 ± 7.0 ml/min/kg.

Male systolic BP fell from 125 ± 5 to 117 ± 9 mm Hg (p<0.05). Male HDL-cholesterol rose 20% to 1.24 ± 0.21 mmol/L (p<0.01). Men drank less alcohol and caffeine at the end of the study year (p<0.05; p<0.01) and more caffeine than women at either time (p<0.01). Women consumed less calcium (19.8±6.0 to 16.1±3.5 mmol/d, p<0.05) and less iron (0.27±0.12 to 0.23±0.10 mmol/d, p<0.05) at the end of the year.

Men and women reported increased interpersonal strain (p<0.05) and decreased self-care (p<0.05), and men perceived increased physical strain (p<0.05) by the end of the year. Women perceived greater responsibility, less help and time to meet work

demands, and less clear authority lines (p<0.05).

Male residents, but not female, became less fit and more fat during the first year of residency. Measures of stress indicated disruption of interpersonal relationships, poor self-care and inability to ∈ngage in stress reduction, and health promotion habits. Women perceived greater responsibility, but less support.

A Computer-Assisted Intervention to Improve the Management of Childhood Asthma

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The successful management of childhood asthma depends on childrens' compliance with medical regimens. Asthma Command is a computer game that teaches children how to manage their asthma. It is tailored to each child's allergens and medications, and gives them practice in making everyday decisions that could affect the frequency and seriousness of attacks. This study evaluated the effectiveness of the game in improving asthma management (measured by the Asthma Behavioral Assessment Questionnaire) and reducing unscheduled medical visits due to asthma.

Of 111 eligible children 7 to 14 years old with moderately severe asthma who were patients at a local municipal hospital, 91 were recruited and randomly assigned to four groups. One experimental group (E1) was exposed to Asthma Command for two years, E2 played the game the first year but not the second year, E3 did not play the first year but played the second year, and the control group (C) was not exposed to the game. Children in E1, E2 and E3 played the game every 2 months in their first year and E1 played "or demand" in Year 2. Complete data (intake, 12 and 24 months) were collected on 71 children and their parents.

ANOVA and multiple regression analyses show that at the end of the Year 1, children in E1 and E2 reported better asthma management than did E3 or C (p=.02). By the end of the second year, children with any exposure to the game (E1, E2 and E3) had fewer unscheduled medical visits for asthma than C children (p<.05). Recency of game exposure may have a greater impact than total dose, since E1 and E3 had the fewest visits (4.5 visits a year versus 10.5 for controls). A significant interaction in a two-way ANOVA revealed that children with poor behavioral adjustment at intake (low scores on the Personal Adjustment and Role

Skills Scale) benefited most. Asthma Command may be a useful tool in helping children manage their asthma and seems particularly effective with children who have poor behavioral adjustment and so are hard to reach with other interventions.

Learning by Teaching: A Resident-Taught Parent Education Oral Therapy Program for Diarrhea Implemented in a Continuity Clinic Setting

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Several recent studies have indicated the need for improved education of pediatricians and parents in the United States on the proper oral therapy (fluids, electrolytes, feedings) for management of acute diarrhea. We initiated a program in which residents in their outpatient clinics educate parents on oral therapy based on American Academy of Pediatrics recommendations.

At the start of the 1989 academic year, residents from all three years of training in their daily continuity clinics completed a questionnaire assessing knowledge and practices in 8 categories related to oral therapy for acute diarrhea and then received a didactic lecture on the subject. While 61 residents filled out an initial questionnaire, 48 were available for an identical follow-up questionnaire 4 months later. During this 4 month interval, residents in two of the weekly sessions (N=19), using a set of printed guidelines, were asked to instruct parents on the principles of cral therapy during well-infant visits. Residents in the remaining three sessions (N=29) were not given formal instructions regarding teaching of oral therapy to families.

Esults showed that residents who actively taught improved in 6 of 8 categories surveyed and achieved significantly better overall improvement scores compared to those receiving conventional teaching (t=2.26, p<.03). The greatest differences were seen in 3 categories: (1) increased percentage of patients treated with oral therapy, (2) knowledge of contraindications to giving oral therapy, and (3) appropriate earlier advancement of feedings. We conclude that active involvement of residents in a parent education program can effectively supplement conventional didactic teaching of residents. Such a program resulted in significant improvement in residents' knowledge and practices of appropriate management of acute diarrhea.

Maternal Understanding of Commonly Used Medical Terms in a Pediatric Setting

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A study was performed to evaluate maternal understanding of commonly used medical terms. All sixty-two pediatric residents at a university based pediatric residency training program participated. They were asked to identify, from a list of 196 medical terms, those terms they believed mothers of their patients would understand without further explanation or definition. Thirty-six terms were identified as "common medical terms" by at least % of the residents. Eleven representative terms were selected from this group (asthma, vitamin, fever, development, flu, kidney, allergy, diarrhea, iron, oxygen, virus). These eleven terms were presented to 100 English speaking mothers of children in a public pediatric health facility where the residents rotate. Mothers were asked to define each term. Each written definition was evaluated for accuracy, based on specific predetermined criteria. The mean number of terms accurately defined was 7.7 (70%), and the understanding of terms was directly correlated with the mother's age and education level. Mothers with a ninth grade education or less had a mean of 5.8 correct definitions and mothers 18 years of

age or younger had a mean of only 5.3 correct definitions.

A significant portion of pediatric residency training often occurs in public health facilities. Our study demonstrates that the population using these facilities fails to understand 30% of the basic medical terms that residents presume are understood. Furthermore, this lack of inderstanding among the younger and less educated part of the parental population rises to 50%. Residency training must emphasize the need for specific explanation of even common medical terms. Understanding of even the most basic medical terminelogy should not be presumed.

Does Physician Attire Influence Parent Satisfaction With Medical Care?

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It is now well established that verbal communication between physicians, parents and children forms the basis of a therapeutic alliance which influences many health outcomes. Considerably less is known about non-verbal processes. Several theoretical studies have suggested certain physician attire may communicate a lack of competence to parents.

The purpose of this study was to determine the impact of physician attire on parents' satisfaction with medical care. To accomplish this we conducted analyses on 209 pediatric visits between pediatric residents and parents with children 5-12 years old. All visits were videotaped to allow for analyses. To measure parent satisfaction we used the Parent Medical Interview Satisfaction Scale (P-MISS), an established 27-item scale with alpha = .95 which measures perceptions of competence, rapport, distress relief, and compliance intent. P-MISS was administered at the end of the visit; parents were unaware of study hypotheses. To assess physician attire we developed a 5 point coding scheme with acceptable interobser ver reliability which categorized specific items of dress. We found correlations to be low between physician attire and each of the 4 2-MISS subscales as well as the total satisfaction score (r = .09, p (2-tailed) = .21). Separating physicians into two groups to compare the most casually dressed residents with the rest of the group also failed to reveal differences in parent satisfaction (T = 1.50, p = .15).

We conclude that physician attire does not influence satisfaction with medical care. While other studies have found attire to be a factor in parent preference for physician, this study differed in methodology by testing the hypothesis in actual clinical encounters and using standardized instruments. Parents' satisfaction with medical care (as measured by the P-MISS) has been shown to be influenced by many verbal and non-verbal factors which appear to be of greater importance than physician attire.

CLINICAL ISSUES

Outpatient Management of Febrile Infants (FI) 28 to 90 Days of Age With Intramuscular Ceftriaxone (CTX)

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A bacterial focus may be demonstrated in 3-8% of FI 1-3 months old with no obvious serious infection on examination. Traditional management often includes admission and parenteral antibiotics pending bacterial culture results. We conducted a prospective study of IM CTX for the cutpatient management of FI 28-90 days old, with fever $\geq 38^{\circ}\text{C}$, and no source on physical examination or screening laboratory tests. After blood, CSF, and urine were obtained for culture, if the infant was nontoxic, the peripheral WBC was $<20\times10^{\circ}\text{/L}$. CSF WBC $<10\times10^{\circ}\text{/L}$, and urine dipstick WBC esterase negative, the FI received 50 mg/kg of IM CTX and were sent home. A second dose was administered 24 hours later

and the FI were followed up by telephone at 2 and 7 days.

Over 33 months (2/87-11/89), 441 $\hat{F}I$ were enrolled. 29 $\hat{F}I$ (6.6%) had a bacterial focus identified during follow-up. Their mean age was 55 ± 17 days, mean temperature $38.9\pm0.6^{\circ}\text{C}$, mean peripheral WBC 11.7 ± 3.3 $10^{\circ}/\text{L}$, mean % band forms $7.0\pm6.3\%$, and mean band count 0.78 ± 0.73 $10^{\circ}/\text{L}$.

Of the 29 FI with bacterial foci, 7 had bacteremia (2 cases of Group B Streptococcus, one case each, E. coli, N. meningitidis, S. pneumoniae, S. aureus, and H. influenza Type B). One infant had a UTI with E. coli bacteremia. 9 had simple UTIs despite negative urine analyses. 10 had bacterial gastroenteritis w/o bacteremia (8 with Salmonella, and one each Yersinia and Campylobacter). In the infants who had stool guiaic or gram stains performed, occult blood or PMNs were identified in 5 of the 7 tested infants. 2 FI had pertussis. 4 of the 8 bacteremic FI fulfilled the published Rochester criteria for low risk of bacterial infection (i.e. normal UA, WBC >5 and <15 × 10 $^{\circ}$ /L), and band count <1.5 × 10 $^{\circ}$ /L). 18 of the 21 (86%) FI with UTIs, bacterial gastroenteritis, or pertussis without bacteremia fulfilled these criteria for low risk of bacterial infections.

At follow-up, all 8 bacteremic infants were afebrile, had sterile cultures, and were given an appropriate course of antibiotic therapy. The infant with S. aureus bacteremia had distal femoral osteomyelitis diagnosed one week after initial visit, was hospitalized, treated, and after one year of follow-up has normal growth of the involved leg. Of the 10 FI with bacterial gastroenteritis w/o bacteremia, 9 were followed at home and 1 required hospitalization due to increasing bloody diarrhea w/o dehydration or toxicity. Of the 10 FI with UTIs, all looked well and had sterile cultures at follow-up; 4 were admitted for IV antibiotics and 5 managed without complications as outpatients. The 2 FI with pertussis were admitted 6-15 days after study entry due to severe spells of coughing. Of the remaining 412 FI w/o a bacterial source, 401 were managed as outpatients and were well at 7 day follow-up. 11 were admitted to the hospital 5 hours to 10 days after study enrollment. All were well at follow-up.

We conclude that for non-toxic FI 28-90 days old, who after a full sepsis work-up do not have a bacterial source identified by physical exam or screening lab tests, IM CTX for 2 days with telephone follow-up may be an alternative to hospital admission.

Lack of Efficacy of Short-term Prednisone, Trimethoprim-Sulfamethoxazole, Alone or Combined, in Persistent Otitis Media With Effusion: Season of Entry as Possible Determinant of Outcome

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Previous trials of prednisone and trimethoprim-sulfamethoxazole (TMP-SMZ) in patients with persistent otitis media with effusion (POME) have shown conflicting results. Duration of effusion, severity of hearing impairment, prior surgery, length of followup, dosage and duration of prednisone, and, especially, antibiotic treatment are some of the factors possibly affecting outcome. We evaluated short-term prednisone, TMP-SMZ, alone or combined, on long-standing effusion (>10 wks) in patients scheduled for myringotomy and ventilating tubes and noted also the possible effect of season of entry [spring (Mar-May), summer (June-Aug), fall (Sept-Nov), winter (Dec-Feb)] on outcome. In a prospective, double-blind, controlled study, 102 patients, ages 1-7, were randomly assigned to one of four treatment groups: a) prednisone 1 mg/kg/day × 5 days, 0.5 mg/kg on the 6th day, and 0.25 mg/kg on the 7th day; b) prednisone in the same dosage combined with 8 mg/kg TMP or 40 mg/kg SMZ, in two divided doses × 7 days; c) TMP-SMZ in the same dosage; cr d) placebo. Mean hearing loss (air bone gap in dB) and tympanogram category were determined at entry, I wk, I mo, 3 mo, and 6 mo. Patients were ranked according to overall improvement score. For overall

effect of season, spring entry patients (n=26) did significantly better than fall entry patients (n=27) (p<.05). No other seasonal pairing was significant. Although TMP-SMZ patients (n=27) showed the best ranking, results were not significant, even at the 10% level. Within severity class (0-14 dB, 15-24 dB, >25 dB) and tympanogram categories, TMP-SMZ patients again did best, although results obtained were not significant.

In our experience, short-term prednisone with or without TMP-SMZ treatment of POME in patients scheduled for surgery does not appear to be effective. Further studies on POME should look at the role of season of entry as a confounding variable, as well as at dosage and duration of antibiotic treatment, and at longterm outcome.

Predictive Value of the Differential Leukocyte Count in Diarrheal Illnesses in Children

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The determination of the etiology of diarrhea is important when specific treatment is available such as with Shigella. The purpose of this study was to evaluate the predictive value of the differential leukocyte count for the etiologic agent of acute diarrheal illnesses. 2095 patients (mean age 28 months) had stool cultures sent from the emergency department from January, 1987 to January 1989. A bacterial pathogen was isolated in 408 (Shigella 177, Salmonella 146, Campylobacter 78, others 7). The charts of all patients with a positive culture were reviewed. The charts of 446 patients with negative cultures (selected using random number table) were reviewed. 50% of the patients with a positive culture and 61% of patients with a negative culture had CBC results. Data was analyzed using the t test and Chi square test.

The total WBC, absolute band count, percent neutrophils, percent bands and band to mature neutrophil ratio were tested at various values for association with etiologic agents. The total white blood cell count and percent of neutrophils were not statistically different among the etiologic agents. The percent bands ≥10% and a band to mature neutrophil ratio ≥1.0 were associated significantly with a bacterial etiology (p<0.0001). Percent bands ≥30% had a positive predictive value (PPV) of 81% for any bacterial pathogen (sensitivity 39%, specificity 18%). Percent bands ≥30% had a PPV of 69% for Shigella versus all other bacterial and nonbacterial etiologies. Percent bands ≥30% had a PPV of 90% for Shigella versus other bacterial agents (sensitivity 63%, specificity 71%). A band to mature neutrophil ratio ≥3 had a PPV of 93% for any bacterial pathogen (sensitivity 42%, specificity 36%). A band to mature neutrophil ratio ≥3 had a PPV of 85% for Shigella versus all other bacterial and nonbacterial etiologies. A band to mature neutrophil ratio ≥3 had a PPV of 99% for Shigella versus other bacterial agents (sensitivity 60%, specificity 93%).

The presence of bands on a CBC is suggestive of a bacterial etiology for the diarrheal illness. Percent bands ≥30% and a band to mature neutrophil ratio ≥3 are highly predictive of a bacterial agent especially Shigella. A patient with diarrhea whose clinical presentation suggests a bacterial etiology and has a band to mature neutrophil ratio ≥3 should be managed presumptively as having Shigella.

The Association Between Infant Weight Gain and Breast Milk Intake Measured by Office Test Weights

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Inadequate weight gain in the breast-fed infant is a common management challenge in pediatric practice. The clinical assess-

ment of breast-feeding adequacy is hampered by the lack of a practical, objective measure of milk intake with breast-feeding. This report provides data to support an association between rate of weight gain in breast-fed infants and milk intake documented

by infant test-weights at a breast-feeding.

319 primiparous women and their term, healthy breast-fed infants were seen twice in the 1st 18 days post partum. Naked infant weights were obtained at each visit using the Sartorius integrating balance, accurate to 0.1 gram. Infant weight gain was calculated in grams per day between visits. Maternal lactation was deemed to be "sufficient" when an infant was fed only breast milk and achieved an average weight gain of ≥28.5 grams per day between the 1st and 2nd visits. Infants gaining <28.5 grams per day returned for a 3rd visit at ≤21 days of age. Final lactation outcome was determined for mothers of these infants based on infant weight gain between the 2nd and 3rd visits. 85% (271/319) of women ultimately achieved sufficient lactation, while 15% (48/ 319) remained insufficient by 3 weeks post partum.

Test-weight data were obtained on a large sub-set of study infants at each visit. Clothed infants were weighed on the Sartorius integrating balance before and after nursing. Weight change with feeding represented milk intake (1 gram = 1 milliliter). Test weight data were analyzed for all infants who sustained suckling for at least 5 minutes and who had not nursed within the preceding 2 hours. 220 infants met these criteria at the 1st visit and 211 infants

at the 2nd visit.

Age in Days

Infant weight change with a breast-feeding ranged from -2.6 gms (due to insensible weight loss) to 148.1 gms. At both visits, infant milk intake at a breast-feeding was associated with final lactation outcome. The mean milk intake among infants of mothers who achieved sufficient lactation was significantly higher than the mean milk intake for infants of mothers with insufficient lactation.

Infant Milk Intake in Grams (Mean ± SEM)

(Mean ± SEM) N Sufficient N Insufficent p value 192 56.7 ± 1.7 28 1st visit $5.7 \pm .09$ 36.3 ± 4.9 .0001 2nd visit. $10.9 \pm .12$ $183 \ 70.6 \pm 1.9 \ 28$ 49.7 ± 4.5 .0001

An isolated test-weight <60 gms at either the 1st or 2nd visit was significantly associated with lactation insufficiency (p<.05 and p<.02 respectively). An even stronger association was found hetween infant milk intake and final lactation status if the testweight was <45 gms at either visit (p=.001 and p<.001 respectively). At the second visit, a mother whose infant consumed <45 gms was 5.9 times more likely to have insufficient lactation than a mother whose infant consumed ≥45 gms (CI: 3.14, 10.99).

These data suggest that intake of breast milk measured by office test-weights is associated with rate of infant weight gain in the first 3 weeks of life. With the availability of an accurate scale, test-weight data performed in the office setting can provide clinicians with objective criteria for evaluating lactation performance. Measuring the "feeding" in a breast-feeding should be part of the clinical evaluation of inadequate weight gain in breastfed infants.

How Do Practicing Pediatricians Manage Febrile Infants?

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Substantial efforts are currently underway to develop accurate clinical prediction models for febrile young infants in order to maximize quality of care and to minimize unnecessary procedures and hospitalizations. In the interim there is considerable controversy about the optimal management of febrile infants. The purpose of this study was to document management of febrile illness by practicing pediatricians and assess the accuracy of clinical judgment in detecting serious illness.

We prospectively gathered information on 308 infants less than one year with fever ≥38.5°C. Fifty-six physicians, members of a statewide network of practicing pediatricians conducting collaborative research, gathered data in six periods of two weeks for one year. The population was predominantly white (78%) and middle class (9% Medicaid). Physicians judged 31.6% of infants <2 months (n = 19) and 24.0% of infants >2 months (n = 289) to be moderately or severely ill. Lab test ordering was very selective and not unexpectedly was higher for younger infants (<2 months) vs older infants (CBC 52.6% v. 14.1%, blood culture 21.1% v 11.0%, LP 15.8% v 1.0%). Only 2 of 19 infants <2 months were hospitalized. Follow-up was obtained on all infants; twenty eight percent of infants required subsequent medical evaluations. Serious illness was rare, evaluations detected only 1 case of bacteremia, no bacterial meningitis, 1 case of viral meningitis and 4 cases of pneumonia. The low incidence of serious illness indicated further analysis was not warranted.

We conclude that practicing pediatricians are very selective in utilizing extensive laboratory testing and hospitalization to monitor even very young febrile infants, but rely on clinical judgment. This study of physician behavior confirms previous reports from surveys of practitioners, but differs markedly from reports of pediatric resident behavior. Because of the low incidence of serious illness in community practice a different threshold for invasive procedures may be appropriate. We estimate a sample size of over 2,000 infants will be needed to answer questions of accuracy of clinical judgment in detecting serious illness in pediatric community practices.

A Randomized Controlled Trial of Cefixime Compared to Amoxicillin for Treatment of Acute Otitis Media

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Cefixime, was compared with amoxicillin in a randomized trial for treatment of acute otitis media. Cefixime was given at a dose of 8 mg/kg/day either as a single dose or in two divided doses, and amoxicillin at 40 mg/kg/day in 3 doses. Bacteriologic outcome was assessed by a second tympanocentesis after 3-5 days of therapy. 106 patients were randomized in the study, and 61 grew bacterial pathogens and returned for evaluation. Outcome did not differ between those treated with once daily cefixime and those given 2 divided doses, so results were combined for analysis. Fisher's exact test (2-tailed) was used.

Pathogens were eradicated in 26 of 33 children (78.8%, 95% confidence limits 64.9 to 92.7%) given amoxicillin and 24 of 28 children (85.7%, 95% confidence limits 72.7 to 98.7%) given cefixime (p>0.50). When only Streptococcus pneumoniae cases were analyzed, bacteriologic cure occurred in 15 of 16 (93.8%) given amoxicillin and 12 of 16 (75%) given cefixime (p=0.333). When Hemophilus influenzae cases were analyzed, cure occurred in 8 of 13 (61.5%) given amoxicillin and all of 9 given cefixime (p = 0.054). Failure of amoxicillin therapy was due to H. influenzae (5 cases, 2 beta-lactamase positive), S. pneumoniae (1 case), and Branhamella catarrhalis (1 case, beta-lactamase positive). Cefixime failures were all four due to S. pneumoniae, although one case had a co-infection with B. catarrhalis. Side effects of diarrhea and nausea were mild in both groups and did not necessitate stopping therapy.

We conclude: 1) Cefixime did not differ in overall efficacy from amoxicillin. In order to show that our difference in efficacy of 7% was statistically significant with a power of 80%, we would have needed to enroll 1018 subjects. 2) Cefixime is more efficacious than amoxicillin for H. influenzae and may be the drug of choice in areas where beta-lactamase producing H. influenzae is very common, or in children failing to improve during amoxicillin

therapy.

Cost/Benefit and Procedure/Benefit Analysis of Infants at Risk for Occult Bacteremia

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We performed a cost/benefit and procedure/benefit analysis of a hypothetical cohort of 10,000 infants at risk for occult bacteremia (OB-age 3-24 mos., fever without a source) evaluated by three currently-acceptable practices: 1) CBC and blood culture (BC) at first visit. Expectant therapy of infants with a peripheral WBC count >15,000. Subsequent visits and work-up dependent on BC results and response to treatment (LP/admit if febrile at follow-up). 2) BC only at first visit. Subsequent visits and work-up dependent on BC results (LP/admit if febrile at follow-up). 3) No laboratory procedures at first visit. If febrile at follow-up, proceed as in 1. We used outcome data derived from a retrospective analysis of 190 infants with Streptococcus pneumoniae OB seen in our institution over an eight-year period which is summarized as follows:

	Treated	Not Treated	
Well at Follow-up	119 (90%)*	32 (55%)*	
Ill at Follow-up	13 (10%)*	26 (45%)*	*p<0.01
Meningitis	5 (4%)**	4 (7%)**	**Not significant
Total	199	58	. 0

We chose to omit OB due to H. influenzce, type b and N. meningitidis since they account for only 15% of patients in our hospital (based on the same retrospective review). We assumed an incidence of 4% OB. The results obtained by means of decision tree analysis are summarized as follows:

Procedure/Method	CBC/BC/Exp.Rx	BC Only	No Labs
$\#BC \pm CBC$	10,000	10,000	180
#LP	68	180	161
#Admit 3 d	50	153	19
#Admit 10 d	18	27	34
(meningitis)			
Cost per patient	\$234	\$239	\$180

We conclude that while observation without laboratory intervention appears to be the most cost effective method, the cost reduction per patient is not significant enough to outweigh the increased number of invasive procedures (lumbar puncture), morbidity, and, perhaps, complications (meningitis). Identification of a high-risk group by means of a CBC and BC and expectant treatment at initial encounter appears to be the most cost effective and procedure effective method of clinical evaluation of infants at risk for OB.

Strategies for Diagnosis (Dx) and Treatment (Rx) of Occult Bacteremia: Clinical and Cost-Effectiveness

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High fever in young children may signify occult bacteremia, which can lead to meningitis and other focal infections. We conducted a clinical and cost-effectiveness analysis for Dx and Rx of children 3-36 mos with T \geq 39.0C. The baseline analysis used data on 950 children in a study of bacteremia and estimates from the literature to evaluate 5 strategies: (1) No Rx; (2) Blood culture (Bcx) alone; (3) Rx+Bcx; (4) White blood count+Bcx \pm Rx (pts with WBC \geq 15 have Rx+Bcx and pts with WBC<15 have Bcx alone); (5) Rx alone. For a hypothetical cohort of 100,000 febrile toddlers, the results are:

Strategy	# of major bacterial complica- tions	# of anti- biotic: rashes	anaphy- laxis	Cost/	Cost/ compli- cation prevented
No Rx	600	0	0	\$ 79	N/A
Bcx alone	390	76	0.5	148	\$70,476
Rx + Bex	312	4040	4.3	144	50,000
$WBC + Bcx \pm Rx$	319	1443	1.7	144	51,246
Rx alone	480	4000	4.0	79	65,833

Using WBC+Bcx ± Rx vs. Rx alone prevents an additional 161 complications at an incremental cost of \$40,373/complication prevented. Sensitivity analyses show that the choice of strategy depends greatly on the effectiveness of initial Rx and the sensitivity of Bcx. When initial Rx is 35% or more effective in preventing compls, Ex alone is more effective than Box alone. When initial Rx is 86% effective, Rx alone prevents as many complications as WBC+Ecx ± Rx at less than 60% of the cost. We conclude that: (1) Rx + Bcx prevents the most complications but $WBC + Bcx \pm Rx$ is almost equally effective and avoids 60% of the antibiotic allergies entailed by Rx+Bcx; (2) while Rx alone is cheapest, its merit depends greatly on the effectiveness of initial Rx. Using a 3% incidence of bacteremia, 24% incidence of major complications, and 20% effectiveness of initial Rx, given the need to prevent antibiotic allergies, we recommend the strategy $WBC + Bex \pm Rx$.

Predictors of Bacterial Illness in Febrile Four-to-Eight Week-Old Infants

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Due to the fear of missing serious bacterial illness in febrile infants younger than eight weeks old, conventional management in the medical center setting is to perform a complete evaluation for sepsis and begin empiric parenteral antibiotic therapy pending culture results. Our study was designed to determine if a combination of clinical and laboratory parameters could predict bacterial illness in those infants whose physical examinations were unrevealing.

All infants between 29 and 56 days old with rectal temperatures more than 38.2°C presenting to a hospital emergency department were enrolled. The attending physician's clinical assessment of the infant was recorded and a complete evaluation for sepsis was performed. Fifteen of the 276 infants enrolled had a source of infection identified before laboratory studies. Of the remaining 261 infants, 27 (10%) had culture positive bacterial infection: urinary tract infection (n=14), bacteremia (n=5), gastroenteritis (n=5), meningitis (n=3). The individual variables of clinical impression of sepsis, peripheral white blood cell count (WBC), band to total neutrophil ratio (BNR), and height of fever were not significant predictors of bacterial illness. However, one or more of the following positives: moderate or ill appearance, WBC > 15,000, BNR >0.20, or abnormal urinalysis, had a sensitivity of 100% (95% CI, 87% to 100%) and a specificity of 47% in predicting bacterial illness. Thus, none of the 110 infants with a negative test had serious bacterial illness.

In our population, the use of clinical signs combined with a CBC and urinalysis could predict all infants with serious bacterial illness. These parameters may aid the practitioner in the evaluation of the febrile 4-to-8 week-old infant.

Occult Abdominal Injuries in Childhood

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Intra-abdominal injuries occur frequently in children who sustain severe multisystem trauma and can carry significant potential

morbidity and mortality risk if unrecognized and untreated. The purpose of our study was (1) to ascertain whether potentially lifethreatening intra-abdominal injuries occur in the absence of multisystem trauma in children, and (2) to determine the usefulness of physical examination and a pediatric trauma score in the assessment of liver or spleen injuries in children. We reviewed the medical records of all patients admitted to a children's hospital who had liver or spleen injuries over a seven year period, recorded the clinical findings, and assigned a Pediatric Trauma Score (PTS) and an Injury Severity Score (ISS) to each child. 77 patients were identified; 55 (71%) were male, 22 (29%) female. The mean age of the patients was 9 years 5 months (±56 months), range 22 months to 20 years 4 months. 54 of 77 (70%) patients had a spleen injury, 18 (23%) had a liver injury and 5 (7%) had both liver and spleen injuries. The mechanism of injury was a direct blow to the abdomen in 35 of 77 (46%), pedestrian struck by a vehicle in 18 (23%), passenger in a motor vehicle accident in 10 (13%), fall in 11 (14%), stab wound in 3 (4%). Patients were managed without surgery in 63 of 77 cases (82%); two died. No significant difference was found between patients with isolated spleen or liver injuries and patients with multiple injuries, with respect to their mean initial pulse. rates (105 vs 107 bpm), systolic blood pressures (116 vs 106 mm Hg), Glasgow Coma Scores (15 vs 13); (p>.05). Fifty-one of 77 (66%) patients received an ISS of 18 or less; 26 (34%) patients received an ISS greater than 18. A strong negative correlation (r = -.80, p = .001) was found between the PTS and the ISS for children with multiple severe injuries (ISS>18); there was poor correlation (r = -.04, p>.05) between the PTS and the ISS for isolated spleen or liver injury (ISS≤18). We conclude that: (1) spleen or liver injury may be present in children without other irjuries and must be considered with a high index of suspicion, and (2) neither the initial clinical findings nor the PTS reliably predict spleen or liver injuries in children with focal abdominal injuries.

Dog Bites in Urban Children: It's the Pits!

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Animal bite injuries are common childhood occurrences which are often attributed to specific breeds of dogs. Pit bulls have recently been implicated as principal perpetrators of these injuries. To investigate this and other epidemiologic characteristics, we prospectively studied all children who presented to The Children's Hospital of Philadelphia during 1989 for evaluation of dog bite injuries. Information was collected from parents, either at the time of visit or by phone on the following day. A total of 165 children were enrolled; the mean age was eight years. Males outnumbered females 1.5:1. Most (60%) of injuries occurred in or around the home and involved dogs known to the patient (76%). Types of injuries included abrasions (33%), punctures (29%), and lacerations (38%). Nineteen bites had associated complications; ten developed infection. Twelve (7%) children required admission to the hospital. Over 20 different pure or cross-breeds were identified as perpetrators; including: german shepherds (N=35), pit bulls (N=33), and mongrels (N=37). Most (53%) animals were contained (i.e., leashed, fenced, in-house) at the time of injury. Fewer (45%) were provoked prior to biting. Significantly more pit bull injuries (94%, p<0.001) were the consequence of unprovoked attacks and involved freely-roaming animals (67%, p<0.01). Children younger than six years were most likely to provoke animals prior to injury (67%) than were older children (35%, p<0.001). Our data indicate that families with young children should be the target of pet safety education and that legislation restricting pit bull ownership should be sought.

Intramuscular vs Intravenous EDTA for Lead Mobilization Testing

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In a prospective stučy we compared urinary lead diuresis following administration of a standard dose (35mg/kg) of edetate calcium disodium (EDTA) by either the intramuscular (IM) or intravenous route (IV). 139 patients were enrolled during the study period. 105 children received IM EDTA (Group I) and 34 received IV (Group II). Group I children were encouraged to drink fluids. Group II children received a 10 ml/kg fluid bolus followed by IV fluids at a rate equal to 11/2 times hourly maintenance fluid requirements. Results from 40 of those in Group I and 6 in Group II were deemed uninterpretable because of incomplete urine collection or inadequate wrine output (<100ml in a 6 hour collection period). The mean age of the children in Group I was 33.6 months compared to 33.1 months in Group II (p=NS). At the time of the mobilization test Group I had a mean whole blood lead of 1.82 umol/ L, while the mean whole blood value for Group II was 1.78 \mumol/ L (p=NS). Results were.

	Group I		Group II		
	Mean	SEM	Mean	SEM	P
Total Urine Volume (ml)	249	20	491	42	<.001
Urine [Pb] (µmol/L)	4.10	.29	2.17	.24	<.001
Total Pb (µmol/TV)	0.87	.069	0.92	.091	NS
Ratio of Total Pb/EDTA dose	.39	.02	.39	.03	NS
Uninterpretable N (%)	40	38	6	17	<.05

We conclude that enhanced lead diuresis does not occur when EDTA is administered by the IV route, despite increased urine output. These data suggest that fixed lead output occurs because only a finite amount of lead is available for mobilization. However, while the IV route is not associated with greater lead output, this method of administration is associated with a significantly higher rate of interpretable results and offers a less painful method of administration.

DEVELOPMENTAL AND BEHAVIORAL PEDIATRICS

Effects of Cocaine Exposure During Gestation on Newborn Neurobehavioral Functioning

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Increasing numbers of pregnant women are using cocaine/crack during pregnancy. It is important to document the effects of that use on their infants immediately after birth. The objective of the study was to compare the neurobehavioral status of newborn infants who had been exposed in utero to cocaine to that of non drug exposed infants. The Brazelton Neonatal Behavioral Assessment Scale (NBAS) was administered within 3 days after birth to four groups of infants: Group 1—infants whose mothers had prenatal care and were positive for cocaine during pregnancy (n=26), Group 2—infants whose mothers were positive for cocaine during pregnancy and the mothers had received an intensive intervention to help them become drug-free before birth (n=14), Group 3—infants whose urine was positive for cocaine at birth and whose mothers had no prenatal care (n=16) and Group 4—a drug-free fullterm group (n=50).

Each infant's NBAS scores were divided into six clusters and the clusters were averaged for each group. ANOVAS were used to analyze the significance of the differences across groups. Significant F scores were obtained on the following clusters: orientation, motor, regulation of state, autonomic stability. No differences

were found on the habituation and range of state clusters. Posthoc comparisons between groups indicated that Groups 1-3 performed significantly worse than Group 4 on all four clusters. There were no systemic differences among the drug-exposed groups.

The results of this analysis suggest that infants who were exposed to cocaine during gestation suffered negative consequences whether or not their mothers had prenatal care and even if there was no drug present in their system at birth. Infants who have difficulty in orienting to and following human faces present a difficult challenge to caregivers. Knowledge of the unique characteristics of these infants at birth may aid caregivers in providing appropriate care for this group of high risk infants.

Antihistamines: Do They Affect Children's Performance?

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Sedation and other central nervous system side effects of antihistamines (AH) could potentially affect learning and school performance. Because no study in children has addressed this issue, we compared the long acting non-sedating AH astemizol (AST) to the classic AH chlorpheniramine (CHL).

94 patients with isolated allergic rhinitis, aged 8-16 years, completed a prospective, randomized, double-blind cross-over study. The study was 13 weeks long, the first pretreatment week served as a baseline. Children were then treated 3 weeks with one medication and after a 6 week wash-out period were switched to the other.

The Continuous Performance Test (CPT); Visual Aural Digit Span Test (VADS); Beneton Visual Retention Test (VRT); Grooved Pegboard Test and Finger Tapping Test, were used to measure attention and concentration, auditory visual short term memory, visual motor integration and fine motor coordination, respectively. These tests were given at the baseline period and at the end of each treatment.

Side effects (sleepiness, nervousness, etc.) were recorded by the child daily, using a linear analogue scale. Compliance with medication was measured by self report, counting unused capsules, and urinary CHL levels. Data were analyzed using the Paired T Test with a $P \le .01$ as the level of significance.

There were no clinically important differences in the results of the performance tests or in the incidence of adverse effects when AST was compared with CHL or when each drug was compared to the baseline. The means for sleepiness for example were, 2.02 SD-2.05 (AST) and 2.12 SD-1.88 (CHL) P-.6.

We conclude that the 2 AH studied are safe for use and neither adversely affects the performance of children.

Psychological Sequelae of Medical Complications During Pregnancy

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Previous studies that assessed the effects of complications during pregnancy have focused on the infants' perinatal courses. Much less is known about the effects of such complications on the mother's perceptions of her offspring. To determine whether mothers with complicated pregnancies are at increased risk of postpartum depression and whether their children are at an increased risk of being perceived as vulnerable, mothers of 1095 children aged 4 to 8 recruited from a stratified random sample of 19 community based pediatric practices were interviewed (94% participation). The sample of mothers was mostly white (77%), married (67%) and educated (57%>HS degree). Mean income was \$30,000.

All 1695 pregnancies were rated by a blinded investigator according to a standardized scale of complications. Of these, 139 (13%) had a severe pregnancy complication such as toxemia or preterm labor. Maternal perceptions of vulnerability were assessed using the 10-item Child Vulnerability Scale which asks parents to rate their degree of worry about their child's health. The offspring were viewed as vulnerable by 24% of the women with severe pregrancy complications and 16% of women without pregnancy complications (RR = 1.5; P = .03). Women with a severe complication of pregnancy were twice as likely to have feared for their child's life compared to those with an uncomplicated pregnancy (37% vs. 18%; P<.0001). Women with a severe complication of pregnancy were significantly more likely to report postpartum depression compared to those without a complication (27% vs. 12%: RR=2.25; P<.0001). These relationships persisted after adjusting for prematurity and neonatal hospitalization.

We conclude that severe pregnancy complications may place a woman at increased risk of postpartum depression and may have important effects on a mother's long-term perceptions of her child's vulnerability to illness.

Acculturation and Compliance With Medical Therapy in Puerto Rican Children With Asthma

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Of the many factors that have been shown to affect compliance with medical therapy, acculturation to mainstream society, a measure of intracultural variability among persons from minority cultures, has not been studied. This project was undertaken to determine the relationship between acculturation and compliance with taking asthma medication in a mainland urban Puerto Rican community. Our hypothesis was that those families who displayed a less acculturated style of adjustment would have higher rates of noncompliance with biomedical therapy than families whose style of adjustment incorporated strategies from both the "Latino" and "Anglo" lifestyles. Parents of 28 Puerto Rican children who attended an asthma clinic were interviewed during a routine (nonurgent) visit. Data concerning medical, health care, demographic, socioeconomic, and cultural issues, including use of folk treatments, and belief in the humoral (hot/cold) theory of illness were collected. Also administered was a standardized instrument that measured acculturation. The dependent variable-compliancewas defined as a serum theophylline level between 7-22 mcg/dl (all children were prescribed daily theophylline). Whereas there were no significant differences between the compliant (n=15) and noncompliant (n=13) groups in many of the variables that have been previously shown to be associated with noncompliance (including severity of illness, length of illness, number of medications, side effects, age of patient, education level of parent), differences were noted in acculturation scores (p=.0165, eta = .449), locale of parental schooling (Puerto Rico vs. mainland, p = .026, OR = 6.67), and whether the child resisted taking his or her medicine (p = .03, OR = 6.19). Acculturation is an easily measured variable that the clinician working in a multicultural setting can utilize when assessing risk of noncompliance. Acculturation stresses intracultural variation and thus avoids the simplistic use of race or ethnicity as a sterotypic variable. Further studies placing acculturation within a multivariate model of compliance are needed.

Factors Motivating Foster Parenting of Chronically III Children

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Foster parents for children with chronic illness or disabilities (FPC) are especially difficult to recruit. Studies have suggested that married couples of lower socioeconomic status having experience with chronic illness or disabilities (CDD), parenting experience and community involvement are well suited for caring for children with CDD. To address this issue, we individually administered a standardized questionnaire to 81 FPC and 39 control foster parents of healthy children (FPH) currently caring for at least one foster child for the last 6 months. We report the factors related to willingness to accept foster children with CDD.

FPC and FPH were similar in being primarily female (97.4% vs 93.8%, p=.7), married (74.1% vs 64.1%, p=.3), not holding jobs outside the home (82.1% vs 79%, p=.7), with a similar mean number of natural children (2.6 vs 1.9, p = .1), mean years foster parenting (9.8 vs 9.4, p=.8), and attending religious services at least once a week (70.2% vs 63.4%, p=.2). Gross family income distributions were comparable. FPC were somewhat younger compared to FPH (mean age 47.2 vs 53.2, p=.02), more likely to be white (43.2% vs 15%, p=.003), have more formal education (HS grad 37%, some college 46.9% vs 35.9%, 15%, respectively, p<.0005), received more income from foster parenting (p=.0001) and more involvement in community activities (76.5% vs 53.8%, p=.012). FPC reported a significantly higher incidence of childhood exposure to a family member with severe physical illness or accident (37% vs 13.2%, p=.008) and alcohol problems (34.6% vs 7.7%, p = .004), but had similar exposure to mental illness, physical, sexual, or drug abuse. Logistic regression analysis using foster parent status as the dependent variable revealed that higher education status (B = .88, p = .006), increasing number of natural children (B=.24, p=.03), white race (B=1.0, p=.07) and childhood exposure to family member with alcohol problems (B=1.3, p = .05) predicted the likelihood of being FPC.

In conclusion, personal commitment based on childhood experiences with illness in the family are important factors associated with foster parenting of children with CDD. Recruitment of FPC would be enhanced if targeted towards well educated, committed individuals who are experienced in raising children.

A Novel Asthma Camp Intervention for Childhood Asthma Among Urban Blacks

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While previous research has shown that asthma self-management programs can be effective, current programs are not widely available or tailored to the unique needs of minority patients, and often require a moderately high level of reading skills and education. Following a needs assessment in 1986, ALADC began a 3 year pilot program to improve the health status of 5-10 yr old urban, black asthmatic children. We hypothesized that participation in a one day asthma camp curriculum, using a collaborative multidisciplinary team approach between University and community-based staff, would provide an effective educational intervention to teach children and their families daily management strategies for asthma. The initial 84 participants (X age = 9.6 years) were predominantly black (93%), male (73%), and from single parent or guardian homes (52.7%). Follow-up interviews suggested that a high percentage of the children were using new techniques such as aerosol/inhaler (78%), breathing exercises (55%), and postural drainage (50.9%). The health status of the children who participated in 1987-88 in the year prior to and following camp attendance was:

	Yr.	Yr. Following*	P-Value
School Days Missed	Prior* 11.8±1.8	5.2 ± 1.4	< 0.001
Emergency Room	: '	,	
(ER) Visits	1.7 ± 0.4	1.1 ± 0.3	0.024
Days Hospitalized	2.1 ± 0.6	$\boldsymbol{0.7\pm0.4}$	0.044
*X±SEM			

After adjustment for differences in period of observation, a similar pattern was found for 1989 camp participants. Overall, participation in this novel program was associated with a clinically significant, 36-69% reduction in school absences, ER visits, and hospitalizations. A randomized trial is planned to further examine the effectiveness of this educational intervention. Thus, this asthma camp program for the instruction of self-management techniques for childhood asthma might serve as a model program for other U.S. cities with high risk inner city black populations.

Neurodevelopmental Outcome in Infant Cardiac Transplantation: The First Four Years

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Neurodevelopmental outcomes of infants who underwent allographic cardiac transplantation between 10/85 and 11/89 were prospectively evaluated by serial neurological examinations and head circumference measurements, speech and audiology evaluations, and serial developmental assessments. 54 infants with uncorrectable congenital heart disease (47 with Hypoplastic Left Heart Syndrome) underwent transplantation 4 hours to 4 months after birth. There are 43 survivors (80%) ranging in age from 3 weeks to 4 years, 86% of surviving infants are neurologically normal, an average of 14 months after transplant. 8 patients had mild neurological findings on examination. These resolved in 50% within the first year of life. Serial head circumference measurements were normal in 94% of patients. Peri-operative cranial ultrasonography revealed no significant abnormalities in any of the infants. This was confirmed by neuropathologic examination in the 11 infants who died. No deaths were due to neurologic causes. Postoperative seizures occurred in 9 infants but 89% of these no longer required anticonvulsant therapy within 12 months after surgery. 92% of infants had normal hearing as assessed by brainstem audiometry evoked response testing or visually reinforced audiometry. 77% of children had normal language as determined by the Sequenced Inventory of Communication Development. Serial assessments using the Bayley Scales of Infant Development revealed an average Psychomotor Developmental Index of 89 (range 5(-130) and average Mental Developmental index of 94 (range 50-124). There was minimal variation in scores as patients matured. Cur findings suggest that the neurodevelopmental outcome of infants undergoing cardiac transplantation is favorable. Postoperative seizures and early abnormal neurological findings resolved in most patients. These data suggest that development was related to pre-existing nervous system factors rather than acute and reversible cardiovascular impairment.

Causes of Decreased Linear Growth Among Homeless Childre■

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We have shown previously that homeless children in New York City have decreased inear growth when compared to domiciled poor children. We hypothesized that social factors not evaluated previously may explain the decreased linear growth.

In order to test this hypothesis, we reviewed the initial visits of

83 homeless children, aged three months to eleven years, who presented to an on-site health clinic at a shelter hotel. The following information was retrieved: patient height, ethnicity, sex, gestational age, birth weight, age, history of chronic illness, medicaid status, maternal age, maternal parity, single parenthood, history of arrest of male parental figure, maternal education, history of foster care placement of the child, and duration of homelessness of the family. Height percentiles were calculated from National Center for Health Statistics (NCHS) standards.

Consistent with prior studies, the height percentile distribution of these children was skewed significantly toward lower values when compared to NCHS standards (p<.001). 59 (71%) had mothers who were high school dropouts, 31 (37%) had male parental figures who were arrested for drug-related and/or violent crimes, 55 (66%) were presently living only with their mother, and 6 (7%) had a history of foster care placement because of child abuse or neglect.

Hierarchical multiple regression analysis, controlling for the variables listed above, revealed that single parenthood, history of male parent arrest, history of mother being a high school dropout, and history of foster care placement are each significantly associated with decreased height percentile (p<.05). Taken together, these four factors account for 20% of the variance in height percentile. Duration of homelessness was not significantly associated with decreased height percentile.

Decreased linear growth among urban homeless children may be explained by certain pre-existing social factors. We are unable to conclude that prolonged exposure to the conditions in the shelters contributes to the linear growth delay.

Growth and Development in Children of Cocaine Abusing Mothers

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Cocaine in all forms is the number one drug of choice among pregnant women, leading to concern about the effects on the fetus and developing child. Records of 70 children with exposure to cocaine *in utero* who were referred for developmental evaluation were reviewed in an effort to determine whether a specific pattern of abnormalities could be discerned.

All children received complete physical exams, neurological screenings and behavioral and developmental assessments based on the Gesell Developmental Inventory, and the Denver Developmental screening test. Documentation of specific drug use was obtained by history. Mean age at referral was 19.2 (S.E.M. = 1.7) months.

All mothers used cocaine in one of its forms with 47% also using alcohol, 14% using opioids, 10% marijuana, and 7% PCP. Mean maternal age (S.E.M.) was 27.1 (.78) years with 25% thirty years and above. Mean birth weight (S.E.M.) for full-term infants was 2808 grams (87.4). Mean gestational age (S.E.M.) was 36.4 (.7) weeks with 44% representing pre-term deliveries. The cocaine exposed children had a mean (S.E.M.) height age percentile (HAP) of 31.5 (4.2) and a mean (S.E.M.) weight age percentile (WAP) of 30 (3.9), while children admitted to our institution for failure to thrive had HAP=9.9 (2.2), p<0.0001 and WAP=6.5 (1.6), p<0.0001. Ninety-four percent had language delay, 62.9% had fine motor delays, 37.1% had gross motor delays, and 54.3% had

cial skill delays. Hypertonicity was present in 30%. Behavioral abnormalities included abnormal play in 58.6%, and hyperactivity in 30%. DSM III criteria for autistic disorder were present in 11.4%.

Growth parameters, though low, were not characteristic of children seen for failure to thrive. Significant neurodevelopmental abnormalities and an alarming frequency of autism were seen. The high rate of autistic disorders previously unreported in children exposed to alcohol or opioids alone suggests specific cocaine effects. Prospective controlled studies with drug testing are essential for documentation.

Prevalence of Home Telephone Service Among Families Using an Inner-City Hospital's Outpatient Services

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Pediatricians base much of their care of children, especially those with chronic conditions, on access to the telephone. In poor communities, however, home telephone service may not be affordable, or families may be wary of divulging their number. We surveyed 91 parents bringing children to an inner-city teaching hospital outpatient department (52 at the resident's primary care clinic, 39 at the children's emergency room) and asked about current and past home telephone service. Confidentiality was assured and no identifiers were collected. Results for the two groups were similar and are combined in the discussion below.

Twenty of 91 (22%) currently had no phone service in their home; 6 of the 20 had never had a telephone at that address, and 14/20 had not had one for 6 months or more. Half said that financial problems were the major reason for not having service. Parents who said that their child had a chronic illness were no more likely to have phone service than those who said that their child was well. Twenty-five of 71 (35%) who did currently have telephones had not had one at some time in the past. Of the 45 who now or had ever lacked service, 39 (87%) were able to find alternative ways to place a call. For only 6 of the 39, however, was the alternative phone in the building in which they lived. Most (26/39) used a phone at a relative's or neighbor's home, with the remainder relying on pay telephones. Less than half of those using pay telephones said that they always felt safe when making a call, compared to nearly 90% of those who used a neighbor's phone (p=.001). Nearly half (35/76, 46%) of families who had phone service now or in the past had unlisted numbers, with a desire for privacy being the most commonly given reason. We conclude that: 1) many inner city families with children (45/91, 49%) do not have regular telephone service, a situation that may require modification of clinical strategies and that strengthens the need to consider telephones as a component of basic social welfare benefits; and 2) clinicians must understand family concerns for privacy before asking for a telephone number.

Can You Spoil an Infant? A Primary Care Survey

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Many parents believe that infants can be "spoiled". The purpose of this study was to determine if there were important subtypes of beliefs about spoiling that might have implications for child rearing practices.

Parents from three different pediatric practices (n=303) completed a questionnaire about spoiling. As defined by the first three questions of the questionnaire—1. Can you spoil an infant (less than 5 months old)? 2. Should you spoil an infant? and 3. Do (or did) you spoil your infant?—four types of spoiling beliefs were predicted:

Type I's believe spoiling cannot occur.

Type II's believe spoiling can and should occur (i.e. it is OK to spoil).

Type III's believe spoiling can and should not occur, but they did spoil their infant anyway. And

Type IV's believe spoiling can and should not occur, and they did not spoil their infants.

The second part of the questionnaire had parents rate, using five point Likert scales, agreement or disagreement with a.) seven definitions of spoiling and b.) beliefs about spoiling's impact on development. The last part of the questionnaire obtained demo-

graphic information.

Results confirmed highly significant differences between spoiling types. Type I's tended to be of higher SES, more educated and white. When compared with the other types, Type I's viewed the defined spoiling behaviors as more desirable and as having a positive impact on a child's development. Type III's and IV's viewed spoiling behaviors as undesirable and as having a strong negative impact on child development. Type II's belief patterns fell statistically between those of Type I and Types III/IV.

With three questions pediatricians can access an important belief system. Parents with Type I and II beliefs are probably at lower risk of misunderstanding their infant's cues and needs. Parents with Type III and IV beliefs may need to be counseled.

Diagnosis of Attention Deficit Hyperactivity Disorder (ADHD) by Primary Care Physicians

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ADHD is the most common pediatric behavior disorder diagnosed and treated by primary care physicians (PCPs). This study examined children diagnosed by 12 PCPs in two small midwestern cities. For 3 months, the PCPs completed screening behavior cisorder checklists on all children between 6 and 12 years of age seen in their practices. Of 457 children screened, 4.8% were diagnosed as having problems with attention deficits and/or hyperactivity; 86% of this group was male. Other behavior problems were diagnosed in only an additional 1.8% of the children screened. The identified children, a control group representative of the entire population screened, and a subgroup matched for age and gender to the inattentive/hyperactive sample received further evaluation. This included parent structured psychiatric interview, teacher behavior ratings, intellectual and neuropsychological assessment, controlled observation of on-task behavior, electronic monitoring of activity, and computer-assisted assessment of attention and impulsivity.

Although 72% of the PCPs identified hyperactive children were diagnosed as ADHD based on parent symptom report alone, only 37% were by teacher symptom report alone. Using either parent or teacher information, 79% received an ADHD diagnosis. Diagnosis agreement between PCPs diagnosis and parent interview was reasonably high for moderate to severe cases (Kappa = .52). but agreement was much lower when compared to teacher report of symptoms (Kappa = .25). Although both physicians and teachers identify approximately 5-7% of children with ADHD, there was clear agreement about diagnosis for only 1.8% of the population. Physicians also rarely identified co-morbidity of other behavioral disorders. Thus, despite more clear symptom definitions in the diagnosis of ADHD, sources of diagnostic information frequently do not fully agree, so that PCPs must learn to obtain systematic behavioral data from as many sources as possible to establish the diagnosis and identify co-morbidity.

EMERGENCY MEDICINE AND CHILD ABUSE

Relapse Following Emergency Room (ER) Treatment for Acute Childhood Asthma: Can It Be Predicted or Prevented?

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We prospectively followed 314 children presenting to and discharged from a children's hospital ER for an acute asthmatic attack to identify risk factors for relapse, i.e., a second ER visit

for asthma within the next 10 days. Parents were surveyed concerning their child's past medical history, triggering factors, drugs taken in the 24 hours prior to the ER visit, home environment, parental anxiety, and sociodemographic variables. Data on severity of the attack, emergency treatment, response to treatment, and drugs prescribed on discharge were extracted from the ER chart.

96 of the 314 children (31%) relapsed, most (68%) within 24 hours. Using multiple logistic regression, a predictive model for relapse was developed on the first 211 patients ("test sample"). The best model contained two variables: (1) the number of ER visits for acute asthma in the previous year (OR = 1.4, 2.0, 2.8, and 3.9 for 1-3, 4-6, 7-9, and \geq 10 visits, respectively, vs 0 visits) and (2) the intake of a short-acting oral theophylline preparation during the course of ER treatment (OR = 0.4, 95% CI = 0.3-0.5). The sensitivity, specificity, and positive predictive value (PPV) of this model for predicting relapse were 67%, 58%, and 40%, respectively. When applied to the subsequent "validation sample" of 103 children, sensitivity was 55%, specificity 74%, and PPV 50%, thus indicating the robustness of the model in our asthmatic population. Based on the total sample, the probability of relapse was 31%. Patients with >4 ER visits for acute asthma in the past year (frequent visitors) had a probability of relapse of 45% vs 20% for nonfrequent visitors The intake of short-acting theophylline during the ER visit reduced the probability of relapse from 50% to 34% in the frequent visitors, and from 30% to 11% in the nonfrequent visitors.

Thus our model improved the clinical prediction of relapse by approximately 50%. It identifies the number of ER visits in the previous year as an important risk factor for relapse and suggests a potentially important preventive intervention: the administration of short-acting the phylline as part of the treatment of the acute attack. This suggestion merits further evaluation in a randomized controlled trial.

Upright or Lying Down: Is One Better for Doing a Lumbar Puncture (LP)?

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Previous studies in meonates evaluating effects of positioning during LP found the similar position optimal. To further evaluate this, we prospectively evaluated the relationship between LP position with cardioresmiratory changes.

Patients, age 1 week to 24 months, were randomly assigned to sitting (S) or lying (L) position and placed on cardiac and oxygen saturation monitors. Easeline and continuous measurements of heart rate (HR) and oxygen saturation (O-sat) were obtained. These parameters were evaluated in regards to patient age, position, time (duration of procedure), and evidence of respiratory disease (tachypnea, (+) chest X-ray).

Our data revealed that mean age $(22\pm29 \text{ v}\ 20\pm24 \text{ weeks})$, baseline O-sat $(99.1\pm3.4 \text{ v}\ 98.6\pm1.3 \text{ torrs})$, total time for LP $(277.6+141.1 \text{ v}\ 242.9+149.1 \text{ sec})$ and evidence of respiratory disease $(3\text{ v}\ 5)$ between (S) vs (L) groups respectively, were not significantly different. Changes of 15 beats per minute or more were noted in 23 (64%) patients; 8 (28%) decreased and 15 (42%) increased. Irrespective of LP position, the infants ≤ 4 weeks of age (neonates) had a significant drop in heart rate $(14.4\pm17.9 \text{ v}\ 6.1\pm7.7,\ p=0.05)$ compared to infants 5 weeks or older. Also the proportion of neonates with respiratory decompensation (desaturation of 5% or more) was 6 of 10 (60%) compared to 7 of 26 (27%) of older infants (p=0.36). Using logistic regression analysis with O-sat $(\leq 4\text{ v} \geq 5\%)$ as the dependent variable and age, LP position, drop in heart rate, time and presence of respiratory disease as independent variables, there was no significant relationship.

This study reveals that neonates tend to show more cardiorespiratory changes than older infants during an LP, but positioning does not appear to be causal. Oximetry and heart rate monitoring is recommended during an LP, especially in the neonate.

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Increased Blood Lead in Children With Nasal, Aural, or Esophageal Foreign Bodies

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Experience in our clinic suggested a high frequency of foreign bodies (FB) in lead-poisoned patients. We investigated the risk of increased blood lead levels in children who place nonlead-containing FB in their nose, ear, or esophagus by prospectively determining venous blood lead levels (Pb), venous free erythrocyte protoporphyrin levels (EP) and environmental risk factors for lead poisoning in consecutive patients presenting to our emergency department for evaluation of a FB. Control patients had Pb drawn for routine screening in our medical clinic. There were a total of 39 study patients with a mean age of 38 mos. and 65 controls with a mean age of 33 mos. There was no significant difference between the two groups in age, sex, race, zip code or the following environmental risk factors for lead poisoning: 1) age of house greater than 25 years 2) peeling paint in the house 3) family or personal history of lead poisoning 4) household member with occupational lead exposure 5) residence near an industrial source of lead. There was also no significant difference in digital sucking or mouthing of nonfood items. The FB+ patients were more likely to have a history of a prior FB (72% vs. 26%, p<.001) and to have a history of swallowing a nonfood item (31% vs. 9%, p<.02). Eleven of 39 (28%) FB+ patients had Pb \geq 25 μ g/ml vs. 4/65 (6%) of FB - patients (p<.01, odds ratio 6.0, CI 1.6-27.6). One patient in the FB+ group required immediate chelation for class IV lead poisoning that was previously unsuspected. The mean Pb was 21 ± 12 µg/ml in the FB+ group vs. 15 ± 6 µg/ml in the FBgroup (p<.001, Kruskal-Wallis H test). There was no difference in mean EP level. We conclude that inner city children with ear, nose and esophageal foreign bodies have increased blood lead compared to controls and may have a greater risk for lead poisoning.

Ought 'Standard Care' Be the 'Standard of Care'?: A Study of the Time It Takes to Administer Antibiotics to Children With Meningitis

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To conform to 'standard of care' (SOC) in Illinois, a physician "must use the skill that is ordinarily used by doctors in similar circumstances. A failure to do so is called malpractice" (Illinois Pattern Jury Instructions 105.01, p.319). However, experts may differ in pronouncements of SOC and sometimes an expert's opinion may have no discernible basis in fact. In such instances how should differences be resolved and how should SOC be determined?

In the context of bacterial meningitis, it has been widely promulgated that administration of antibiotics begin within 30-60 minutes of evaluation of the patient. We tested whether this opinion of SOC corresponded to actual 'standard care' delivered in 2 unaffiliated institutions. Using a retrospective chart review we examined the time from ER presentation to initiation of antibiotic therapy (ABTIME) for patients with meningitis from Jan. 1987 to Sept. 1989. For Hospital A (n=38) mean ABTIME was 2.70 ± 1.61 hours (range 0.58-6.66). For Hospital B (n=36) mean ABTIME was 2.79 ± 1.73 hours (range 0.45-7.76). The difference between hospitals was not statistically significant (t=0.23). For comparison, we reviewed records of 77 patients ≤ 3 months old admitted to Hospital A with 'r/o sepsis' (mean ABTIME = 3.21 ± 1.96 hours, p=NS vs meningitis patients, ANOVA).

Conclusions: 1) In 2 unaffiliated institutions 'standard care' for ABTIME in meningitis was 2.70 and 2.79 hours; 2) Expert opinion that SOC for ABTIME differs significantly from 2.7 hours cannot be supported by data; 3) This approach may have broad applicability—insofar as 'standard care' can be determined from data, 'standard care' and 'standard of care' ought to be one and the same.

Local Anesthesia With Lidocaine in Infant Lumbar Punctures: Effect on Pain Response

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We conducted a randomized, controlled trial to determine if lidocaine given locally before spinal needle insertion reduced the pain response of infants during lumbar puncture. The study was done over a six month period in the Children's Hospital Emergency Room. Thirty infants, 0 to 6 months of age, had continuous cardiac monitoring and their cries were tape recorded. The infants were randomly assigned to receive either a lidocaine injection (1 cc of a 1% solution) locally at the site of needle insertion, or to be in a control (no injection) group. A maximum heart rate change was calculated by subtracting the baseline heart rate at the start of the procedure from the maximum heart rate recorded while the spinal needle was inserted. The length and proportion of time spent crying was calculated for three periods: 1) from placement on the bed to spinal needle insertion, 2) duration of spinal needle insertion, and 3) the duration of the total procedure (1+2). The two groups were similar for sex, age, level of the resident performing the lumbar puncture, and presence of parents. Lidocaine did not make the lumbar puncture more difficult as measured by the numbers of attempts, bloody spinal fluid (greater than 500 RBC's/mm²), or length of time to obtain spinal fluid once the spinal needle was inserted. We found no significant differences in heart rate changes or crying measures between the two groups, thus we were unable to demonstrate that lidocaine decreased the pain response of infants during lumbar punctures.

Rapid Screening for UTI in the Emergency Department

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To evaluate the clinical utility of a urine dipstick for nitrite (NI) and leukocyte esterase (LE) as a screening test for UTI, the clinical presentation and urine of 491 children whose ED physician ordered a urine culture were examined prospectively. Overall, 9% (45) of children ages one month to 19 years had UTI's ($\geq 10^5$ CFU [clean catch] or $\geq 10^3$ CFU [cathed] of urinary tract pathogen(s)). The ROC curves of dipstick LE (r=0.81) and laboratory microscopic exam for WBC's (r=0.83) were not significantly different in detecting UTI's. Dipstick results of small (+1) or moderate (+2) LE had both good sensitivity (69%-71%) and specificity (90%-91%) and were comparable to ≥ 10 WBC's on microscopic exam. The presence of urinary NI had lower sensitivity (49%), but high specificity (95%). If both moderate LE and NI were present on dipstick, the relative risk of having a UTI was 10.43 (95% CI, 6.58 to 16.55).

Rapid detection of UTI's in babies <2 years is more difficult since they don't always exhibit classical clinical signs, void more frequently, and often had lower colony counts since their urines were obtained by catheter. However, the presence of either small LE or NI on dipstick had 64% sensitivity and 95% specificity (PV+60%) for this group, as compared to 91% and 81% respectively for children ≥3 years with classical symptoms (PV+43%).

If urine sediment was not clear to visual inspection or the urine dipstick had either small LE or NI, all except one UTI in babies were detected (96% sens, 59% spec, PV + 21%). Laboratory microscopic analysis for the presence of any WBC's or bacteria also had 93% sensitivity, but lower specificity (32%) for this group. Although the relative performance and interpretation of rapid testing for UTI's varies by age, method of urine collection, and clinical presentation, it appears to be as good a screening tool as microscopic urinalysis in a pediatric emergency setting.

Accuracy of Tympanic Thermometry in a Pediatric Emergency Department

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Presence of fever is an important physical finding in the evaluation of the pediatric patient. Tympanic thermometry (TT) is a new technique which is described as measuring body temperature by measuring infrared radiation from the tympanic membrane. The purpose of this report is to assess the accuracy of TT in the pediatric emergency department.

Following an inservice program, nurses performed TT in 599 consecutive patients who presented to the pediatric emergency department at BCH. Patients had TT performed in both ears regardless of the diagnosis. Of the 599 children, most were male (55%), black (63%) and young (15% < than one year, 14% between 1 and 2 years of age). More than 1°F difference between each ear was found in 15% and between 0.5 and 1°F difference in 30% of the patients. There were no differences in the number of discrepancies (>1°F) for children less than one year of age compared to children between one and two years of age (15% vs. 18%, p = .75). 33 of 54 children with unilateral otitis media had discrepant TT (>0.5°F) with the involved tympanic membrane significantly more likely to have the higher temperature (p<0.01). For children less than three months of age (n=14), 2 had temperatures less than 100.4°F in one ear but greater than 100.4°F in the other. For children between 3 and 24 months of age (n=161), 11 (7%) had temperatures less than 102°F in one ear but greater than 102°F in the other.

We conclude that tympanic thermometry provides an inaccurate measurement of core body temperature. Before adopting any new technique for temperature evaluation, physicians should determine if they are accurate. Clinicians should rely on rectal temperatures in patients when core temperature is an important part in the evaluation of that child.

Emergency Department Pediatric Telephone Advice

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To assess the accuracy of emergency department pediatric telephone advice, a mock scenario, simulating a lethargic 5 week-old with fever to 102°F and meningitis was used to monitor the responses of 61 randomly selected emergency departments (E.D.'s) nationwide, half of these departments being affiliated with pediatric residency training programs. All hospitals were given identical chief complaints—"My baby has been having a fever all day and I can't seem to get it down." Research technicians who administered the calls were familiar with details of the case and instructed to provide only specific informatior requested by

the respondent. All calls were monitored by two investigators, and written records were kept monitoring whether any of 11 predetermined key historical questions were asked and documenting the disposition advice given to each caller. Forty-eight calls were answered by a nurse and 13 calls by a physician. Thirtynine (72%) of the 54 E.D.'s that gave out medical information over the phone advised the patient to be seen by a physician, while only 33 (61%) of the E.D.'s suggested that the child needed to be seen the same day. Ten (19%) programs neglected to ask the age of the child, while 8 programs (15%) neglected to ask the height of the temperature. Few programs took historical information assessing irritability (4 programs), intake (11 programs), urine output (8 programs), or breathing pattern (6 programs). Several scenarios were encountered where despite taking a thorough history documenting fever, irritability, and lethargy, the patient was not advised to seek medical attention. More E.D.'s affiliated with pediatric programs suggested that the patient needed to be seen today (73% vs. 50%), although differences did not achieve statistical significance (p value = .08). These data serve to highlight inconsistencies and inadequacies of pediatric telephone advice currently offered by emergency departments.

Skull Fractures in Young Children: Do Characteristics of the Fractures Clearly Distinguish Child Abuse From Accidental Injuries?

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Studies of skull fractures in young children have suggested that complicated fractures-depressed, diastatic, or multiple-are characteristic of child abuse and occur infrequently in accidental injuries. These studies, however, have been limited by the inclusion of only seriously injured children (e.g. children who have died of abuse), so that the full spectrum of injuries due to abuse or accidents has not been adequately examined. To examine the types of fractures in a broader spectrum of cases, we reviewed the medical records and radiographs of all children <36 months of age who were diagnosed with a skull fracture at Yale-New Haven Hospital over a 5-year period. Each case was retrospectively reviewed and rated by 2 clinicians and independently by 2 pediatric radiologists; a consensus rating was then established by all 4 raters. A 7-point scale with specific criteria was used: abuse included the ratings of "definite," "probable," or "possible;" accidents included 3 similar ratings; cases with insufficient data were rated as "unknown."

Of 93 skull fractures, 80% were in children <1 year of age. The consensus ratings were: 25 (27%) abuse, 57 (61%) accidents, and 11 (12%) "unknown." Of the abuse cases, 16 (64%) had a positive skeletal survey or a confession by an adult, and 6 (24%) had evidence of an intracranial hemorrhage. Of the accidental cases, 54 (95%) were due to falls, and 57% of the falls were from heights of <4 feet.

Complicated skull fractures occurred in 36% of abuse cases (9/25) vs. 21% in accidents (12/57) (p>.05). Of cases with complicated fractures, 7 of 9 abuse cases had a history of no fall or a minor fall, while 7 of 12 accidental cases fell from a height of >4 feet. The majority (64%) of abuse cases did not have complicated fractures, but instead had the same types of linear fractures of the parietal bone that occurred in accidents.

We conclude that although complicated skull fractures occur somewhat more commonly in child abuse, the most common type of skull fracture in both abuse and accidental injuries is an uncomplicated linear fracture. Reliance on evidence of a complicated fracture as a marker of child abuse will result in a substantial under diagnosis of this serious problem.

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Risk Factors for Neglect and Foster Care Placement in Infants of Substance Abusing Women

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In an ongoing intervention program on the prevention of abuse and neglect in infants of substance abusing women, the characteristics of families who were reported to child protective services (CPS-Group 1) and whose infants were placed in foster care (FC-Group 2) within the first 9 months were compared with those whose infants remained in the mother's custody (Group 3).

Data are presented on the first 43 families: 40% of the women were HIV positive, 80% had a history of IV drug use, 65% had a history of incarceration. At the initial visit 95% of the infants were in the care of their mother, but by 9 months of age only 67% were still in the mothers care. 22 (53%) of the families had CPS reports made during this period and 12 (28%) of their infants had been placed in FC, 7 due to maternal incarceration, 4 for neglect related to continued drug abuse and 1 because of maternal hospitalization for depression.

Significant differences in the women in Gr1 and Gr2 compared to those in Gr3 were that they were: older (mean ages 26.4 yr & 28.1 yr VS 23.7 yr), had higher total abuse scores (220 & 207 VS 164) and higher subscores for distress on the Child Abuse Potential Inventory, given prenatally and higher depression scores on the Parent Stress Index at 3 months. There was no difference in the mother's perception of social supports and in family cohesiveness or adaptability. The mean birth weights of the infants in Gr1 & Gr2 were significantly lower than those in Gr3 (2780 gm & 2554 gm VS 3075 gm).

Among substance abusing women, those who are older, depressed, less able to handle stress, and further challenged with low birth infants are more likely to engage in high risk behavior that undermines adequate care giving and results in CPS reports and foster care placement.

Sexual Abuse Characteristics Are Not Independent Predictors of Behavior Problems in Sexually Abused Children

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Studies of outcomes in sexually abused (SA) children (SAC) have been flawed by small populations, selection bias, unvalidated methods, and confounding variables. To evaluate SAC prospectively, we obtained information by interview and validated questionnaires from 154 SAC ages 4-12 yrs within 8 wks after they presented for pediatric evaluations of SA and again 6 mos later. Parents of 110 (71%) of the study SAC completed Child Behavior Checklists (CBCLs) at 6 mos. More children with follow-up were insured (74% v 54%, p = .04), but SAC with and without follow-up did not differ with respect to age (7.3 \pm 2.6 v 7.5 \pm 2.5 yrs), sex (80% v 73% female), race (64% v 75% black), identity of abuser (30% v 35% close relative), or duration of abuse (55% v 52% \leq 1 mo).

The SAC's CBCL scores at 6 mos for behavior problems (BP) and 4 subscales [internalizing (INT), externalizing (EXT), depression (DEP), sex problems (SXP)] were compared to standardized scores by age and sex. SA boys <6 yrs were normal on all 5 scales. SA girls <6 yrs scored high on BP (57.9 v 48.2, p<.001), EXT (55.4 v 49.8, p<.03), and SXP (63.7 v 60.6, p<.005), normal on INT, and not tested on DEP. SA boys \geq 6 yrs scored high on the 4 scales tested: BP (62.3 v 50.5), INT, EXT, and DEP (p<.001 for all differences). Girls \geq 6 yrs scored high on all 5 scales (BP 64.3 v 50.6, p<.001 for all 5 comparisons).

When sociodemographic variables and descriptors of the SA and subsequent prosecution were entered into stepwise regression models for BP, INT, and EXT, health insurance status was the only predictor of BP (p=.003, $R^2=.08$), INT (p=.0003, $R^2=.1$), and EXT (p=.04, $R^2=.06$).

Poorer outcomes in SAC have previously been associated with older age of child and specific features of the abuse (e.g., intimate contact, longer duration). We found that these factors did not predict BP when confounding was controlled. Characteristics of children and their families (e.g., parental coping, family function) may be more important predictors of BP in SAC than characteristics of the SA itself.

Interobserver Evaluation of Alleged Child Sexual Abuse Victims With Focal Concave Hymenal Variations

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Forty-nine female children and adolescents who were evaluated for allegations of child sexual abuse were found to have focal concave hymenal variations (clefts/notches). Colposcopic photographs of the hymenal anatomy were shown to five experienced "blinded" examiners. They were given only the age and ethnicity of each patient and were asked to classify the findings into one of following six categories: 1) benign; 2) benign with reservations; 3) uncertain; 4) suggestive of trauma; 5) trauma; and 6) technically inadequate. There was no communication between the examiners during the rating process. Following classification, the patients were analyzed using the Sexual Abuse Medical Assessment Profile (SAMAP) data base containing demographic, historic, physical examination and laboratory data.

10.2% (5 of 49) were predominantly rated as "benign" (at least 4 of 5 raters designating categories 1 or 2). 55.1% (27 of 49) were predominantly rated as "trauma" (at least 4 of 5 raters designating categories 4 or 5). 8.2% (4 of 49) of cases were predominately rated as technically inadequate. There was a wide scatter of ratings in 26.5% (13 of 49). Within the "trauma" group, there were 16 cases (32.7% of all cases) where all five raters were in agreement. These cases with highest interobserver agreement of "trauma" had the following characteristics: 1) clear history of penile-vaginal contact in 56.3%; 2) clear history of digital-vaginal contact in 56.3%; 3) clear history of vaginal penetration in 75%; 4) clear history of ejaculation in 18.8%; 5) clear history of pain in 62.5%; 6) clear history of bleeding in 31.3%; 7) physical finding of posterior hymenal concave variation in 75%, anterior in 18.8%, and lateral in 6.3%; and 8) accompanying hymenal rim narrowing in 87.5%.

The most prevalent correlates to interobserver agreement for "trauma" were history of vaginal penetration with pain and the finding of a posterior hymenal concave variation with accompanying hymenal rim narrowing.

PREVENTION AND EPIDEMIOLOGY

The Effect of Exercise and Cigarette Use During Pregnancy on Fetal Growth

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The effect of moderate exercise during pregnancy on the newborn infant is unclear. The purpose of this study is to determine the effect of moderate exercise during pregnancy on birthweight (BW), head circumference (HC), and length (L). Because of recent data that the energy expenditure of nicotine is significantly enhanced during moderate exercise, a second goal is to explore

the interactive effects of exercise and cigarette use on growth.

As part of a study investigating the effect of maternal health behaviors and pregnancy outcome, 1226 women were enrolled consecutively as they registered for prenatal care. The majority were young (73% 18-29 years old), minority (66% Black, 18% Hispanic), poor (64% <\$1000/mth) and had completed high school (59%). 22% (275) exercised at least once a week during pregnancy. Among the exercisers, the mean number of days/wk of exercise was 2.10 (S.D. ±1.16), 62% reported average exercise of at least 1 day/wk, 34% 2-4 days, and 4% 5+ days.

Bivariate analyses revealed an adverse association of average number of days/wk of exercise and BW (B=-44 grms, p=.01, 95% CI=-77,-10) and L (B=-.021 cms, p=.03, 95% CI=-.39,-.02), but no significant relationship to HC. Multivariate analyses, conducted to control for confounding variables, showed a small adverse association between exercise and BW (E=-22 grams, p=.07, 95% CI=-47,2). No significant associations were found between exercise and HC or L. An adverse interactive effect of cigarette use and exercise on BW (B=-16 grms, p=.05, 95% CI=-32, -.10) and HC was found (B=-.06 cms, p=.02, 95% CI=-.12, -.01). Among the 537 smokers, exercising 2+days/wk during pregnancy was adversely related to BW (B=-163 grms, p=.01, 95% CI=-284, -41), but not HC or L. Exercising one day was not associated with BW, HC or L. Among the nonsmokers, no significant associations emerged.

We conclude that (1) moderate exercise during pregnancy has a small adverse effect on birthweight and (2) exercise among cigarette smokers exacerbates the known adverse effect of cigarette use. This may be due to increased energy expenditure resulting in fetal hypoxia or increased caloric utilization.

Incidence of Illnesses Prompting Physician Visits Among Children in Day Care

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To compare the incidence of illnesses prompting a physician's visit to a health maintenance organization in Houston among children in home care (HC), day care homes (DCH), and day care centers (DCC), we studied a cohort of 270 children, ages 2 to 36 months who participated as healthy controls in a case-control study on the etiology of diarrheal illnesses. Data on household demographics, socioeconomic characteristics, and day care attendance were obtained by parental interview. Each child's medical record was later reviewed regarding illness visitations, antibiotics prescribed, presence of chronic condition, and immunization status for the eight-week period surrounding the interview.

Forty-two children attended DCC, 72 were in DCH, and 156 were in HC. The average number of children per DCC was nine, and for DCH, three. The relative risk (RR) for new episodes of illness prompting a physician's visit among DCC children as opposed to children in HC, was 2.50 (p<.0001) and for those in DCH, 1.09 (p=.30). Respiratory tract infections accounted for 78.6% of physician visits. For upper respiratory infections (URI), including otitis media (OM), only DCC children had an increased risk (RR=2.72, p<.0001). Acute and serous OM was present for 43.2% of illness visits, with excess risk carried only by DCC children (RR=3.81, p<.0001). Antibiotics were prescribed for 35.7% of children in DCC versus 7.1% and 8.2% for children in DCH or HC, respectively (p<.001). The average number of days of antibiotic therapy prescribed for DCC children was 19.9 days and differed significantly from DCH children (4.0 days) and HC children (4.6 days) (p<.001). Given the proportion of children in day care, 19% to 31% of the total burden of URI and OM, respectively in this population was attributable to day care attendance.

Immunization Problems Identified in Hospitalized Preschool-Age Children

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Approximately 95% of school-age children are fully immunized, due to forced immunization compliance prior to school entry. Fewer preschool-age children are fully immunized, however, because of the lack of a routine enforcement program. We conducted a six-month prospective study at a county hospital to determine how frequently hospitalized children 2 months to 6 years of age are deficient in recommended immunizations, and how often deficiencies are corrected prior to discharge or at the first followup clinic visit.

At the time of hospital admission an immunization history was obtained from parents by a pharmacist assigned to the hospital's pediatric unit, and verified by examining the patients' immunization card and public health department immunization record. Patients were considered deficient (DEF) if they were ≥1 month behind in recommended immunizations, and indeterminate (IND) if parental information could not be documented.

Of the 336 children in the study, 167 (50%) were DEF; 68 (20%) were IND; and 101 (30%) were appropriately immunized for their age. Among the 94 patients older than 36 months, 5 (5%) lacked DTP/OPV, 6 (6%) lacked MMR, and 48 (51%) had not received Hib. Among the 242 children 36 months of age or younger, 60 (25%) lacked DTP/OPV; 26 (11%) needed MMR, and 35 (14%) lacked Hib. Admission immunization histories obtained by house officers identified immunization deficiencies in 45 (27%) of the total 167 DEF pts. Deficiencies were corrected in only 4 pts prior to discharge, despite the presence of contraindication to vaccine administration in only 7 patients. To date, 30% of DEF pts have failed to keep their followup clinic appointments, and of the patients reporting to clinic, action to correct existing deficiencies has been documented in only 21%.

We conclude that preschool-age children admitted to county hospitals are often deficient in immunizations. Efforts should be made to more vigorously pursue immunization histories and implement corrective actions prior to discharge of hospitalized patients.

Home Phototherapy for Treatment of Exaggerated Neonatal Jaundice Enhances Breast-Feeding

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The feasibility and effectiveness of home phototherapy have been established, but the length of that therapy, its effect on breast-feeding practices, and its expense need further investigation. To address these issues, a retrospective case-control study was made on otherwise healthy, full-term neonates. To identify infants who had been treated for jaundice, records from seven private pediatricians' offices, a private medical equipment leasing company, and two Salt Lake City hospitals were reviewed for a two-year period. Of the 178 eligible infants, 48 hospital-treated and 48 home-treated babies were randomly selected for study. Data were collected by chart review and a telephone survey of the children's parents. Babies treated in hospital had higher mean bilirubin levels at the start of treatment (20.6 mg/dl vs. 17.1 mg/ dl; p<.001), a faster drop in bilirubin level once treatment was initiated (4.5 mg/dl drop in the first 24 hours vs. 2.1 mg/dl; p<.001), and were treated for a shorter period of time (2.8 days vs. 4.1 days). Mothers of infants treated in hospital were more likely to stop breast-feeding during the period of phototherapy (42.2% vs 9.5%; p<.002) and less likely to resume breast-feeding (80% vs 100%; p<.02) than women whose babies were treated at home. No infants treated at home required admission to the

hospital. The expense for phototherapy was 5 times greater for the hospital group. The results of this study indicate that home phototherapy is less expensive, less efficient, but equally effective as hospital treatment, and that breastfeeding practices may be enhanced in the home setting.

Access to Health Care of Homeless and Other Poor Families

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To evaluate health access and health services utilization of homeless families we selected a systematic sample of 194 homeless families from ten shelters in Los Angeles and of 195 housed, poor families from the same geographic regions of Los Angeles selected from welfare offices.

Both samples were predominantly of minority race (70% vs 85%) and relied primarily on Medicaid for their health insurance (61% vs 96%). However, more homeless families than housed poor families were currently uninsured (26% vs 2%, p<.001), had lost health insurance over the past year (50% vs 21%, p<.001) and spent a greater percentage of the past year uncovered by health insurance (means 22% vs 6%, p<.001). Homeless families were much less likely to report a regular provider for preventive care (81% vs 94%, p<.001) or for sick care (72% vs 95%, p<.001). Moreover, of those reporting a regular provider, the homeless were more likely than the housed poor families to use emergency rooms or clinics rather than private offices for both preventive care (35% vs 15%, p<.001) and sick care (37% vs 26%, p<.05). Barriers to health care more frequently prevented homeless families from obtaining care (38% vs 28%, p<.05). Logistic regression analyses revealed that, after controlling for differences of race, insurance type, loss of health insurance, child health status and sex, homeless families were much less likely to have a regular health provider for sick or well care.

These findings suggest that homeless families have greater problems of access to health care than other poor families, which are related to lack of insurance, lack of a regular primary care provider and other barriers. Programs to aid homeless families should address these deficiencies.

Advising Parents to Stop Smoking: Pediatricians' and Parents' Attitudes in Private Practice

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Pediatricians are in a unique position to address the issues of smoking prevention and smoking cessation with patients and their parents. We surveyed VT pediatricians and parents of their patients in order to assess attitudes about giving and receiving smoking cessation advice. We mailed a questionnaire to 91 pediatricians in VT and received 72 valid responses. Forty percent of pediatricians routinely take a smoking history from parents and 11% record this information in the child's chart. Most pediatricians (94%) report advising 60% of smoking parents to quit, and spend an average of 4.4 minutes doing this. Barriers to giving smoking cessation advice were lack of time (42%), feeling ill at ease (25%), feeling that parents did not expect this advice (25%), and lack of reimbursement (7%). Only 8.5% of pediatricians had received training in giving smoking cessation advice, but 87% were willing to learn brief methods.

Subsequently, we randomly chose 6 solo and 6 group practices and interviewed 676 parents in pediatric offices. The average age

was 32, 34% were women; 49% were never smokers, 30% former smokers, and 21% current smokers, with an average of .5 smokers per household. Current smokers were significantly younger and had less education than former and non-smokers, and were less likely to agree with statements about the adverse effects of passive smoke on infants and children (p<.0001). Most parents (56%) felt that pediatricians should give quit smoking advice to parents, and 57% of smoking parents said they would welcome this advice. Only 27% of current smokers said the advice would bother them, and less than 10% had more negative reactions. Sixteen percent of current and former smokers reported receiving quit smoking advice from their pediatricians. Pediatricians and parents agreed on the best opportunities to give quit smoking advice (prenatal visit, well baby visits, and visits for acute respiratory infections). Since 93% of smoking parents said they intend to quit smoking sometime, and since pediatrician-delivered quit smoking advice would be acceptable to them, it would be worthwhile for pediatricians to learn brief methods of delivering such advice.

Prior Approval in a Pediatric Emergency Room

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Managed care plans designed to serve low income populations are widely promoted as an effective strategy to improve the quality and control the costs of medical care by reducing unnecessary specialty and emergency room (ER) care through the use of primary care physicians (PCP) as case managers/gatekeepers. The purpose of this study was to evaluate, by means of medical record review and survey of pediatricians and ER staff, gatekeeping (prior approval) for children using the pediatric ER of one large urban public hospital (Boston City Hospital).

Over a 6 month period, 337 children, insured under managed care plans that required authorization from the PCP in order to receive treatment, presented to the ER. The majority (85%) received their primary care at community health centers and the hospital's outpatient clinics. Most visits (73%) were made when primary care sites were closed. According to nursing triage assessment, 48% presented with urgent or emergent conditions, and 23% had a history of chronic illness. Despite the creation of an elaborate and costly system for gatekeeping, only 13 (4%) patients' requests for ER care were denied: 3 were seen in the ER without authorization, 6 received the recommended follow-up and 4 were not seen in follow-up.

29 participating PCP's (74%) and 19 ER staff (63%) responded to a survey regarding their experience and attitudes toward prior approval. The majority of PCP's and ER staff found the gatekeeping policies for after hours visits burdensome and inappropriate for a variety of reasons. The low refusal rate observed was due in large part to physicians' reluctance, because of clinical, ethical and legal concerns, to deny care to a child already in the ER.

This study identified multiple problems with the implementation of prior approval policies and suggests that on-site gatekeeping for children living in poverty and cared for at public facilities may not result in the anticipated benefits in patient care or cost savings unless primary care alternatives to the ER can be provided at less cost and with equal availability.

Children Riding in the Back of Pickup Trucks: A Neglected Safety Issue

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Motor vehicle trauma is the leading cause of death in children in the United States. Only a few states possess safety laws or

restrictions for passengers who ride in the back of pickup trucks. A retrospective review of medical records for a 40 month period revealed 40 patients whose injuries were a direct result of being a passenger in the cargo area (bed) of a pickup truck. The mean age of these patients was 7.75 years and their ages were equally distributed between 0-4, 5-10, and 11-16 age group. There was a 3.4/1 male to female ratio. Seventy-three percent of patients were injured as passengers in the bed of an open pickup truck while 27% of patients were injured as passengers in an enclosed pickup truck. The mean injury severity score was 11.3. Seventy percent of the patients had injuries that involved head trauma. Fifty-two percent of the patients who were admitted to the hospital were admitted to the intensive care unit. Sixty-two percent of the patients who were injured were injured in accidents that involved a crash, while 38% were injured in non-crash incidents. Ninetythree percent of the incidents occurred on paved roads, while only 7% occurred on non-improved roads. Eighty-eight percent of the injuries occurred during the warm weather months of April-September. A highway safety survey showed that only 17 states were noted to have any type of restrictions for passengers riding in the back of pickup trucks. Seventy-one percent of those were included in the child restraint laws. Data from the National Highway Traffic Safety Administration shows that death from riding in the back of a pickup truck is disproportionately a pediatric problem. The sales of compact pickup trucks jumped approximately 300% between 1980 and 1986 and it appears that their use is primarily as transportation or recreational vehicles. Physician and public awareness of this dangerous type of transportation needs to be increased.

Barriers to Pediatric Referrals in Managed Care Systems

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Anecdotal evidence suggests that children's access to pediatric subspecialty and inpatient care is hampered by barriers imposed by managed care systems. To identify such barriers and determine if they adversely affect children's health, a survey of American Academy of Pediatrics Fellows (n = 1600) was conducted during the winter of 1989. The survey compared the barriers to referral in managed care and traditional fee-for-service systems. The response rate was 79.1% (n = 1264). Of those pediatricians in direct patient care (n = 956), 71.4% participated in a managed care plan.

Pediatricians referred patients in managed care systems somewhat less frequently than in traditional pay systems: 8.7% reported that they referred managed care patients to subspecialists less often and 6.9% reported that they referred managed care patients to inpatient care less often.

Over 20% of pediatricians with patients in managed care systems had at least one referral to a subspecialist denied in the previous year; 10.2% had at least one referral to inpatient care denied. Of those who had referrals denied, approximately 35% reported that the denial resulted in compromising the patient's health.

Pediatricians who experienced denied referrals were more likely to identify administrative barriers, physician panel/hospital restrictions, and pressure to refer to adult care than those with no denied referrals.

Pediatricians experienced more barriers in discounted fee-forservice plans (PPOs) than in pre-paid capitated plans (HMOs). Pediatricians were more likely to report administrative and physician panel/hospital restrictions when the majority of their patients were in PPOs rather than in HMOs.

These data suggest that utilization management programs, such as those used in managed care systems, may limit children's access to pediatric subspecialty and inpatient care. Further study may help determine to what extent children's health is compromised as a result.

Ambulance Utilization by Homeless Children

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Homeless children living in New York City's shelter system account for many visits to our Pediatric Emergency Service. We hypothesized that homeless children utilize ambulances differently than domiciled children. Over a one-year period, the following information was retrieved from the records of all patients arriving by ambulance: age, residence, diagnosis and disposition. Residence and disposition were collected from all other records. Diagnoses were categorized into the following groups: URI, lower respiratory infection, gastroenteritis, serious infections, asthma, neurological, poisoning, psychosocial, other minor medical, other major medical, sprains/strains, lacerations/contusions, MVA without major trauma, fractures, microsurgery, head trauma, other major trauma, and surgical-non trauma.

Homeless children accounted for 2137/23357 (9.1%) visits. 211 (9.9%) of these homeless visits resulted in admission versus 1581 (7.5%) of the domiciled group (p<.001). 425/2137 (19.9%) homeless children arrived by ambulance versus 999/21220 (4.7%) domiciled children (p<.001). Among transported patients, 93/425 (21.9%) homeless children were admitted versus 319/999 (31.9%) domiciled children (p<.001).

Hospital admission was used as a measure of illness severity. After controlling for age and diagnostic groups, multiple regression analysis demonstrated that diagnostic groups, especially URI, accounted for almost half of the 10% difference in admission rate between transported homeless and domiciled children (p<.01). Nevertheless transported homeless children were still admitted at a significantly lower rate than transported domiciled children (p<.05).

Overall, homeless children were admitted at a significantly higher rate than domiciled children. However those transported by ambulance were admitted at a significantly lower rate. This lower admission rate was due to a diagnostic case mix of lower acuity and possibly to less severe illness within diagnostic groups. This information suggests the need for the development of alternatives to ambulance usage in the transportation of homeless children to health care facilities:

Injuries in Daycare: A 5-Year Perspective on Who Incurs Them and Why

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A study of all injuries experienced by enrollees in a daycare center over its 5½ year history was conducted. "Injury" was defined as any event, intentional or not, that resulted in a physical mark on the child's body or cessation of his activity (prior to the event) for at least 5 minutes.

In 66 months, there had been 194 enrollees who had amassed 3695 child-months. The 101 boys experienced 166 injuries (1.6/boy) and the 93 girls experienced 124 (1.3/girl) injuries. Of the 194 enrollees, 46% incurred no injuries. The five most common injuries were falls (49.0%), bites (16.6%), collisions (8.6%), being struck (7.2%), and being scratched intentionally (6.6%). There were no differences in injury occurrence by age, length of time as an enrollee, or by sex except that boys were more likely to be bitten than girls. Bruises were the most common medical sequelae (41.4%), followed by abrasions (29.0%), lacerations (18.6%), nosebleeds (3.8%), foreign bodies (3.4%), fractures/dislocations (2.8%), and tooth injuries (1.0%). The head was the most common body part injured (61.7% of injuries). There was little variation of injury type or medical sequelae from one year to another or by season. Over 80% of the injuries required only local wound care or

reassurance; only 6% of injuries required a physician visit and only 1.5% required immediate transport to a hospital or physician's office.

Twenty-seven percent of the boys and 20% of the girls incurred 78% of all boy injuries and 65% of all girl injuries, respectively. Compared to enrollees who incurred no injuries, this subgroup did not differ by age or length of time as enrollees, but were more likely to have evidence of psychosocial stressors in their lives.

This study demonstrates that injuries in daycare are overwhelmingly physically minor. However, it also demonstrates that injury occurrence might not be random but might also be related to psychosocial factors in the child's and family's lives. Caretakers would be wise to inquire about such adverse factors (such as divorce, illnesses, change of residences, deaths, abuse, family violence, etc) routinely.

Families Who Seek Care for the Common Cold in a **Pediatric Emergency Room**

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To characterize the demographics and expectations of families who use a large inner city hospital emergency room (E.R.) for the evaluation of children with common colds, a self-administered questionnaire was distributed to parents of children who presented to the E.R. with the complaint of a "cold". 190 questionnaires were completed. The mean age of the children was 3.4 years and the median age was 1.5 years; 91% were black; and 51% were male. The children were generally healthy: 78% of parents rated their child's health as good or excellent. 81% of parents indicated that the cold had been present for at least three days, and 69% reported that their child had a fever.

72% of parents indicated that ensuring that their child had no other illness besides a cold was their first or second most important reason for coming to the E.R. The most common response to the question of what parents felt was the most important thing that might be done for their child in the E.R. was: a physical examination. The second most common response was the doctor giving the parents reassurance and advice. Only 8% felt that the writing of a prescription was most important.

A discharge diagnosis was available for 74% (140) of the children. 51% were diagnosed as having only a cold. The remaining children were diagnosed with various infections such as otitis media (18%)

or pneumonia (14%), or in 6% of cases—asthma.

We conclude that inner city families are appropriately using medical services for the evaluation of children with colds. They are bringing in young, often febrile, children who have been sick for several days to ensure that the children have no other illness but a cold. In fact, half the children did have another diagnosis assigned besides a cold.

GENERAL POSTER SESSION

Correlation of Maternal and Child Blood Lead Concentrations

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Because of its potential use in identifying women with elevated lead levels, who, as a group, carry increased pregnancy risks, such as miscarriage, premature delivery and late fetal death, the correlation between lead levels of children age 9 months to 6 years and lead levels (Pb) of their mothers was investigated.

Blood lead levels were measured in 94 mother-child pairs recruited from an urban population. A standardized questionnaire designed to elicit demographic data and risk factors for lead exposure was administered to each mother. The mean maternal Pb of $0.39 \pm 0.17~\mu$ mol/L was significantly different from the mean child Pb of 0.58 ± 0.26 µmol/L (p<0.01). Individual child and maternal lead levels were significantly correlated (r=0.34, p<0.001). Maternal Pb was regressed against the corresponding child's Pb and the slope of the best fitted line for the data was significantly different from zero (p<0.001). On multiple regression analysis using maternal lead concentration as the dependent variable and including the child's Pb, maternal age, smoking history, whether the child was in day care, school or home with the mother during the day, and if lead had ever been found in the current residence, only the child's Pb was significantly related to maternal Pb (B=0.22, p=0.002). Four percent of the mothers reported that lead had been found in their current residence at some time in the past.

The range of child Pb seen in this study, 0.14-1.5 \(\mu\text{mol/L}\), limits the generalization of the results to the population of mothers whose children have high lead levels. However, the data indicates that maternal lead levels correlate with those of their children when the child's Pb is in the moderate range, probably because of shared environmental exposure. Thus children with high lead levels may pinpoint households in which women of child-bearing age should be screened, a practice that could contribute to

preventive prenatal care.

Holter Monitor and ECG Abnormalities in Children With HIV

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Clinically significant dysrhythmias and sudden cardiac deaths have been reported in adults with HIV infection. Although we have seen 2 children with AIDS die sudden cardiac deaths, there has been little research about the cardiac complications, particularly conduction system abnormalities, of pediatric HIV disease. Therefore, we studied 15 children, aged 4 to 9 years, with congenital HIV infection in an ambulatory setting to determine the prevalence of Holter monitor and ECG abnormalities, and to relate any abnormalities to other clinical findings. All 15 children had symptoms of at least one P-2 subclass in the CDC classification system for pediatric HIV infection, and 12 met CDC case definition criteria for pediatric AIDS. Twenty-four hour Holter monitoring was performed on 15, and 10 also had ECGs. These were evaluated using published standard criteria for age.

Holter monitoring was abnormal in 3 of 15 children, 2 with isolated ventricular premature beats (VPBs) and 1 with sinus tachycardia (ST). The ECG was abnormal in 4 of 10, the abnormalities including ST, left axis deviation, right axis deviation (RAD), incomplete bundle branch block (IBBB), and T-wave changes. Only 1 child had both an abnormal Holter and ECG: VPBs on Holter and ST, RAD and IBBB on ECG. This child, who had no cardiac symptoms at the time of the study, did have cardiomegaly by chest x-ray and has since developed symptomatic congestive heart failure (CHF). One other child had cardiomegaly and symptoms of CHF at the time of her studies: her Holter was normal, but her ECG showed RAD and T-wave changes. Two of 3 children with Holter abnormalities and 2 of 4 with abnormal ECGs had no other evidence of cardiac involvement. Together Holter monitoring and ECG were abnormal in 6 of 15 HIV infected children, 4 of them without other indication of cardiac involvement. Serial Holter monitoring and ECGs may be routinely indicated for children infected with HIV to detect subclinical heart disease that

can be progressive.

Compliance With Childhood Cholesterol Screening in a Health Maintenance Organization (HMO)

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In view of the importance of hypercholesterolemia in the etiology of arteriosclerotic disease in later life, diagnosis and intervention early in childhood is of particular relevance in an HMO where preventive care is a high priority. To identify children at risk for hypercholesterolemia, 1,160 children above age 2 years being given routine examinations had a questionnaire completed by the parent concerning family history of hypercholesterolemia and early arteriosclerotic disease. Random cholesterol testing at the time of exam was done in those with a positive family history because of evidence in a pilot study that compliance was poor if patients were asked to return for a fasting specimen. Of the 529 patients (46%) with a positive family history in which cholesterol testing was advised, 369 (70%) had the test performed; 93 (25%) of these had high values (>95th centile) and were so informed by mail with further testing recommended. Of these 93 children with initial high cholesterol levels 35 (38%) did not appear for retesting, 33 (36%) retested normal and 25 (27%) retested high. Thus, only 2.2% of the children examined, and 4.7% of those with a positive family history were identified as candidates for intervention for nypercholesterolemia. Of special interest are the 30% of cases with positive family history, and 38% with high cholesterol levels, who did not follow through with recommended testing. Thus, even in an organized health care system where preventive care is emphasized and there are no financial barriers, compliance with a cholesterol screening program is poor, and proactive methods must be devised to identify and manage children at risk for the complications of hypercholesterolemia.

Medical Management of Persistent Middle Ear Effusion

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The efficacy of prednisone for 7 days plus sulfamethoxazole with trimethoprim (SMZ/TMP) for 14 days was compared with SMZ/ TMP alone in the treatment of persistent middle ear effusion (MEE). Pneumatic otoscopy, tympanometry, and audiology documented the status of the MEE at entry into the study, and two weeks after therapy. Clearing in both ears or in one when only one was involved was called complete resolution; clearing in one of two affected ears was called partial resolution. Fifty-two patients were enrolled in a randomized, double-blind controlled clinical trial comparing the two regimens. The 2 week outcomes of 24 prednisone + SMZ/TMP treated patients were: complete-18, partial—3, and unchanged—3. The 2 week outcome in 28 SMZ/ TMP patients was: complete—8, partial—4, unchanged—13, acute otitis-3. (P<.02 for complete resolution). Patients whose MEE failed to clear were crossed over to the alternative regimen. The 2 week outcomes of the 18 patients who received prednisone + SMZ/ TMP after the crossover were: complete-10, partial-2, unchanged-3, acute otitis-1, and no follow-up-2. The 2 week outcomes of the 6 patients who received SMZ/TMP alone after the crossover were: complete-2, unchanged-4. The combination of oral prednisone for 7 days and SMZ/TMP for 14 days is more effective than SMZ/TMP alone in the medical management of persistent MEE.

Use of Clinical Observation Scales Following Antipyretic Therapy to Predict Serious Illness in Febrile Children

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The evaluation of young febrile children remains controversial. The diagnostic value of the child's clinical appearance before or after antipyretic therapy has not been fully defined. We hypothesized that 1) the clinical appearance of febrile children without recent antipyretic therapy at the time of presentation would predict serious illness and 2) the clinical appearance of the children who initially appeared ill assessed I hour after receiving acetaminophen would further refine the prediction of serious illness. Children ≤24 months seen in the clinic or emergency department with a rectal temperature ≥38.3°C and who had not had antipyretics in the previous 4 hours were enrolled. After the initial clinical appearance was assessed using the Acute Illness Observation Scale (AIOS) (McCarthy, 1982), 15 mg/kg of acetaminophen was given orally. If the initial AIOS was ≥10, a second rectal temperature and AIOS were measured 1 hour later. Laboratory data, physical findings, and diagnoses were recorded. Phone follow-up was done on day 5. Serious illness was defined as: 1) documented bacterial disease, 2) significant abnormalities of electrolytes, blood gases, or chest x-ray or CSF pleocytosis, or 3) illness requiring extended in-patient therapy.

195 children were enrolled, with a mean age of 10.5 months. 17/ 195 (8.7%) were seriously ill. 62/195 appeared ill at presentation (AIOS \geq 10). 14/62 children who initially appeared ill were seriously ill. The mean initial AIOS was 12.2 in the seriously ill group compared with 7.9 in children without serious illness (p=.001). For the 62 children who initially appeared ill, 1 hour after the administration of acetaminophen the mean temperature in the seriously ill group was 38.8°C compared with 38.4°C in children without serious illness (ns). However, the mean repeat AIOS was 13.7 in children with serious illness compared with 10.0 in the children without serious illness (p=.004).

Children with serious illness generally appear more ill than those without serious illness both before and after acetaminophen. We conclude that a careful clinical assessment using the AIOS before and after acetaminophen is a useful adjunct in the evaluation of young febrile children.

Temperature Relationship to Distance and Flow Rate of Warmed IV Fluids

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Warmed intravenous (IV) fluids are commonly held to be useful in resuscitating a hypothermic patient. We postulated that heat losses from IV tubing would be too great in the emergency room setting, at usual flow rates in children, for this to be beneficial.

To evaluate this, we used a 500 ml bag of 0.9% Sodium Chloride, (NS) Abbott IV tubing, soluset, and life-care pump, a Flo-Tem II blood warmer, and Mallinckrodt Hi-Lo temperature monitors and sensors. Probes were inserted one cm into the IV tubing-one inside the warmer, the others at five, 25, 45, 65, 85, and 105 cm distal to it. Probe accuracy is within 0.1°C. Fluid was warmed to 37°C. Ambient temperature was 20°C.

NS was run through our system at rates from 20 to 1000 cc/hr. Temperature readings were made each minute until the volume of fluid required to flush the tubing had gone through, and temperature readings had stabilized.

The fluid remained warmer than 32°C up to 105 cm at rates of 1000 and 750 cc/hr. At rates of 125 cc/hr or less, at a distance of

greater than or equal to 25 cm, the temperature was less than 32°C. The table shows the relationship between distance and temperature at a selection of our flow rates.

Flow Rate

Distance	1000 cc/hr	125 cc/hr	75 cc/hr	40 cc/hr	20 cc/hr
5cm	$36.5^{\circ}\mathrm{C}$	$35.1^{\circ}\mathrm{C}$	$33.8^{\circ}\mathrm{C}$	33.1°C	$30.8^{\circ}\mathrm{C}$
45cm	34.8°C	$28.6^{\circ}\mathrm{C}$	$26.3^{\circ}\mathrm{C}$	24.1°C	22.6°C
105cm	$33.3^{\circ}\mathrm{C}$	$25.1^{\circ}\mathrm{C}$	$23.5^{\circ}\mathrm{C}$	22.7°C	22.4°C

Implied is that at flow rates usual in pediatrics, a patient would need to be connected to a fluid warming device by a length of IV tubing shorter than is either practical or customary in an emergency room setting.

Highly Mobile, Previously Homeless, and 'Hidden Homeless' Children: How Prevalent in a Pediatric **Primary Care Setting?**

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Much attention has focused recently on the plight of homeless families in America, and several studies have documented the medical and mental health problems of homeless children. Little attention, however, has been directed to the children of families which are either highly mobile, previously homeless, or "hidden homeless"-groups that also may be at risk. To examine the prevalence of such children, we administered a questionnaire to 55 unselected parents waiting to see a pediatrician at a universitybased primary care center that serves an inner-city population. The parents were asked about their family's current living arrangements, moves, and use of emergency housing. The mean age of the parents was 27 years. The number of people in the current household ranged from 2 to 13 (median: 4). Forty-one (74%) of the families had a child <3 years of age. The majority of the sample were minorities (Black or Hispanic) and poor (over 90% had Medicaid).

In the previous two years, 23 families (42%) had not moved at all, 14 (25%) had moved once, and 18 (34%) had moved at least twice. Overall, 13 (24%) had been previously (N=10) or were now (N=3) in emergency housing. Of the 18 families who had moved ≥2 times, 10 had been in emergency housing.

During additional interviews with 45 of the parents, several housing patterns emerged: 1) Twenty-six parents (57%) have had stable housing, have recently moved from their parents' home to their own apartment, or have moved independently to a new apartment for reasons such as fire or the need for a larger apartment, 2) Ten parents (22%) have always lived with their own parents, and 3) Nine parents (20%) have been moving in with various family members or friends, a group previously described as the "hidden homeless."

We conclude that the majority of patients at an inner city pediatric clinic have had at least one change of residence in the previous two years, and that nearly one quarter have experienced emergency housing. We also have identified a substantial group of families described as the "hidden homeless." Pediatricians and researchers need to identify patterns of housing and address their impact on the health and development of children.

Physician Immunization Practices

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Recent declines in pertussis immunization among young children in Utah poses a serious problem. A 1987 survey of parents found

that greater than 30% of one-year-olds were not adequately immunized. Postponement because of illness was cited as the reason for incomplete immunization in 66% of these children. The purpose of this study was to examine physicians' immunization practices and their opinions regarding declining immunization rates. Fifty-two of 103 physicians attending the Intermountain Pediatric Society 1989 Annual Meeting returned questionnaires regarding immunization. Of the respondents, 85% were general pediatricians, and 84% practiced in the Intermountain West. Most physicians stated that the DTP vaccine was contraindicated if the child had a history of seizures or neurologic disorder (69%), or if there were a history of past major reactions to the DTP vaccine. Physicians frequently deferred vaccination for temperature >38° (94%), for ear infections in afebrile children (74%), for colds (46%), for prematurity (78%), and for heart problems (88%). Although 78% could determine from their records if a child was receiving vaccines, only 22% had a method for contacting parents of children whose immunizations were incomplete. While more than half of the respondents (52%) felt the main reason parents don't immunize their children is concern about side effects of the vaccine, only 16% felt children were not immunized because of illness at the time of the visit to the doctor. The results of this study indicate that many physicians delay immunizations for minor illness; few have a method for contacting parents to ensure timely immunization; and, most reported delaying immunization in prematures and patients with heart disease who may be at increased risk of complications if they develop pertussis.

Do Diabetic Children and Their Parents Talk About the Complications of the Illness?

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Medical providers currently emphasize the importance of following a fairly strict regimen of self-care to prevent the complications of diabetes. However, little is known about the extent to which diabetic children are informed about these potential complications and even less is understood about the communication between these children and their parents that focuses on these issues. Thus, the purpose of the present study is to investigate the extent to which diabetic children and their parents discuss the potential complications of diabetes.

Thirty-seven children between the ages of 7 and 13 years with a diagnosis of insulin-dependent diabetes (duration ≥1 year) and their mothers were interviewed. The semi-structured interviews were conducted separately for the children and their mothers at home. Of the mothers interviewed, 92% (n=34) reported that their children were aware of potential complications. However, only 43% (n = 16) of the children interviewed reported an awareness of the existence of these complications. Moreover, only 30% (n = 11) of the children talked with their mothers about complications. Of all the children interviewed, only 16% (n=6) reported a conversation with their fathers. A median split was conducted on the ages of the children (median age = 10 years), and as expected, older children tended to be more knowledgeable about complications than younger children.

Despite the fact that almost all mothers reported communicating with their children about potential complications, the children did not concur. We conclude that parents and children have different views about the child's knowledge of complications and the extent of communication. Clinicians should help parents both to understand the extent of their child's knowledge of complications and to be more effective in communicating about the disease.

Home Monitoring of Sickle Cell Crisis Pain

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Vaso-occlusive crisis (VOC) pain is the most frequent problem encountered by patients with sickle cell disease. As part of a study of behavioral intervention for this illness, we examined the natural history of the pain and its impact on developmentally important activities by using a home diary system for daily self report by patients over the age of 7. Diary ratings included occurrence and intensity of VOC pain and school attendance.

Data were evaluated on 18 children (ages 8-17 years, M=12.9) with a history of frequent VOC (at least 1/month). The children participated an average of 10.3 months, yielding a potential pool of 5,850 diary days. Completed diaries were received for 4,756

days, giving an average compliance of 81.3%.

On average, patients had 2 VOC episodes per month (range .5-5), with a duration of 4 days (range 1-9). Patients reported VOC pain on 33% of all days (range 3-97%). Only 18.5% of days with VOC pain involved hospitalization; on the remaining 81.5% of days, the pain was managed at home. However, some patients managed pain mostly in the hospital, whereas others rarely came to the hospital for pain management. There were no differences between frequently and infrequently hospitalized patients as far as frequency, length, or average intensity of VOC. Despite the low average rate of hospitalization, school was missed on 41% of days with pain.

Conclusion: a daily diary is a viable system for gathering prospective ambulatory data on a long term basis with children with chrcnic illnesses. The majority of VOC pain is managed at home; despite this, the pain frequently results in absence from school. The prevalence of home pain management and the impact of frequent school absences must be considered in the planning of

intervention strategies for these children.

Pediatric Motor Vehicle Related Trauma: Patterns of Injury

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This study was designed to compare patterns and severity of injury among children hospitalized as a result of motor vehicle related occupant, bicyclist and pedestrian events. Data were taken from a multi-hospital monitoring system and the coroner's office in a single urban county, population 2.2 million, from April 1987-March 1989. A standardized questionnaire was completed for each case by abstracting information from the medical record and interviewing the parent/guardian. Injuries were coded using the AIS-85. The Chi-square test of significance and analysis of variance were used. The sample consisted of 547 children, 32% occupants, 22% bicyclists and 46% pedestrians. Intracranial/facial injuries exceeded all other anatomic sites for all 3 events: 56% for occupants, 59% for bicyclists and 63% for pedestrians, but were not significantly different between events. Second in frequency were lower extremity fractures, 15% occupants, 45% bicyclists, 32% pedestrians, significantly different between events. Third were internal torso injuries, 16% occupants, 18% bicyclists, 20% pedestrians, NS between events. Mean MAIS was significantly different between occupants and pedestrians, 2.31 v. 2.61, but not between pedestrians or occupants and bicyclists (2.59). Significant differences between occupants and bicyclists as well as pedestrians, were found with respect to mean number of anatomic sites of injury, overall number of injuries and hospital days, with pedestrians and bicyclists being greatest. Pedestrians had the most fatalities (20), followed by occupants with 13 and bicyclists with 6.

In conclusion, the majority of children hospitalized for motor vehicle related trauma were pedestrians. Head/face injuries predominated and did not differ by event. Bicyclists and pedestrians sustained more lower extremity injuries and were more severely injured than occupants. Some reductions in trauma could be realized through the use of bicycle helmets and increased restraint use. However, additional interventions are necessary to reduce the toll of motor vehicles on children's health, especially in the area of pedestrian injuries.

Physician Knowledg∋ and Attitudes About Daycare

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With more than 50% of women with young children working, daycare has become an important issue. No study to date has examined physicians' attitudes and knowledge of daycare issues.

A 25-item questionna re was sent to randomly chosen board-certified family practitioners and pediatricians in District 3 of the AAP (NJ, PA, DE, MD, WV). The questionnaire was designed to elicit information about the physician's training about daycare issues, frequency of discussion during office visits and attitudes regarding specific medical and developmental issues of daycare.

A total of 338 physicians responded and reflected the general population of pediatricians and family practitioners in the region. Thirty nine percent of the total sample stated they felt uncomfortable discussing daycare issues, and 85% felt their training in this area was inadequate. Those who felt more comfortable were more likely to be pediatricians than family practitioners ($\chi^2 = 9.3$; p = 0.01). Forty-three percent reported rarely or never discussing daycare during an initial visit. There was an association between discussion of daycare and younger physicians ($\chi^2 = 19.95$; p = 0.02), female physicians ($\chi^2 = 17.45$; p = 0.001) and pediatricians ($\chi^2 = 33.43$; p < 0.0005).

Physicians indicated strong feelings about controversial issues related to daycare. For instance, 77% of responders stated they felt the best type of day-are arrangement for a 6 month old infant was in-home care. In addition, 37% were either neutral or agreed with the statement that separation anxiety was more pronounced in children raised in day-are. Seventy percent prescribed rifampin as prophylaxis for Haerzophilus influenzae disease after a single case in a daycare setting.

This study revealed that physicians have had little training about daycare issues, frequently feel uncomfortable and spend little time discussing the subject. In addition, they seem to have definite attitudes about medical and psychological aspects of daycare which are currently unresolved. More formal training should be focused on issues of daycare.

Maternal Perceptio∎ of Offspring Size Among Hispanics

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Several studies have shown that Hispanic populations in the United States exhibit increased levels of obesity compared to non-Hispanic Whites. It is possible that relatively high weight is considered "normal" among these groups because of culturally determined perceptions of ideal body size. We undertook a study of how Hispanic parents of children aged 6 months to 12 years perceive their offspring's physique having hypothesized that extremes of body weight among children may be misjudged because of these culturally determined perceptions of body size. Data were collected during the Hispanic Health and Nutrition Examination Survey (HHANES) between 1982 and 1984, and included maternal perception of child's weight and anthropometric

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measures for both mother and child. The child's physique was expressed as a normalized (z) score for the weight/height ratio (BMI). Of 105 Mexican-American children whose mothers considered them underweight, 57% were below the 25th percentile for BMI. In this group, mothers who were themselves overweight (>25th percentile) were less likely to recognize underweight in their children than mothers of low to normal weight (χ^2 =8.84 p=0.012). Among 759 children whose mothers considered them to be of normal size, 190 (25%) fell beneath the 25th percentile for BMI and 16% were above the 75th percentile. In this group, mothers correctly classified the size of their offspring. Of the 99 children whose mothers considered them overweight, 81 (82%) exceeded the 75th percentile for BMI. However, underweight mothers in this group were less likely to recognize obesity in their offspring than normal or overweight mothers (χ^2 =6.66 p=0.036).

These data suggest that maternal perception of child's size is significantly affected by size of the mother. Further research is needed to determine the role of influences such as poverty and acculturation on this phenomenon.

Prenatal Determination of Demographic and Attitudinal Factors Regarding Breastfeeding in an Indigent Population

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Demographic and attitudinal factors influencing the decision of feeding practice were evaluated early in pregnancy by survey of 307 women in a low risk prenatal obstetric clinic at a publicly funded hospital in Houston, Texas. Subjects responded to 17 demographic and 24 attitudinal questions. Twenty-five percent of the completed surveys were in Spanish. Of the total sample, 26.7% planned to breastfeed, 48.2% planned to bottle feed, and 25.1% planned to do both. Racial classification revealed blacks 36.4%, whites 29.2% and hispanics 30.8%. Multiple logistic regression analysis revealed six prominent independent risk factors for bottle feeding. The most significant variable identified was lack of support from a significant other (i.e. husband, mother, other relative or friend) which produced a prevalence ratio (PR) of 456.3. Other attitudinal variables achieving independent significance were disagreement with the statements "breastfeeding protects against disease" (PR=4.0), "breasts were made for breastfeeding" (PR=8.0), and "I want to know more about breastfeeding" (PR=120.0). Significant demographic variables identified were completion of less than twelfth grade (PR = 32.1), and age less than 35 years (PR = 43.3). These findings indicate the importance of significant others and suggest that future educational programs may require their inclusion to increase the prevalence of breastfeeding in this population.

Joint Topic Sessions With APS/SPR

ADOLESCENT MEDICINE

Oral Contraceptive Use, Serum Cholesterol, and Dietary Intake Among Adolescents

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The purpose of this study was to determine effect of low dose oral contraceptives (OC) on serum cholesterol (Chol) in adolescents and the role of dietary intake on lipid level of girls who are on OCs. Adolescents 12-16 y.o. were assessed at the beginning (base) and after 6 months of OC use for fractionated Chol (performed by VAP method), ht, wt, activity level and dietary intake. At base visit, each girl was provided with individual nutrition counseling, given a handout of high Chol foods and instructed on foods to avoid and to increase their physical activity. 26 girls (mean age 14.8 y.o.) participated in this study. Total cholesterol (T-Chol) at base was 170 ± 28 mg %; 12/26 (46%) had levels greater than 170 mg %. T-Chol at 6 mon was 186 ± 36 mg %; a mean rise of 14 ± 37 (p<.05). In 9/26 (35%) a rise of >20 mg % in T-Chol was observed and in 8/26 (31%) 6-mon level was lower than the base. A rise in 6-mon T-Chol was not associated with having high level at base. A significant rise in LDL-c (86 ± 21 to 97 ± 27 ; p = .04) was observed with minimum rise in HDL-c. Over the 6-mon, ideal body weight increased by mean of 4 lbs (NS). Dietary intake showed a significant decrease in keal (2937 to 2290; p<.01), in saturated fat (satfat) (39 mg to 28 mg) and in polyunsaturated fat (23 to 17 mg). Activity levels were low and did not change (mean of 1.2 out of 4

In an attempt to determine effects of dietary intake on the Chol level changes, variables in girls with T-Chol increase of >20 mg % were examined and compared with that of the rest. In this high risk group of 9 girls, mean T-Chol rise was 54 ± 19 mg % (167 mg % at base, 221 mg % at 6-mon; p<.0001); rise was most significant in LDL-c (p<.0001) but HDL-c and LDL/HDL ratio also rose (p=.02 and .01, respectively). Dietary intake also changed favorably, especially a decrease in satfat (41 to 23 mg; p<.005).

From this preliminary study of 6 months we conclude: 1) low dose OC use of 6 mon was associated with >20 mg % rise of T-Chol in 35% of subjects; rise was in all fractions but most markedly in LDL-c, 2) dietary counseling was effective in changing eating behavior but its effect on Chol·level is yet to be determined, 3) activity levels of adolescent girls were low and resistant to counseling, and 4) in 46% of subjects T-Chol level at baseline was >170 mg %.

The Course of Splenomegaly in Infectious Mononucleosis

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The risk of splenic rupture in patients with infectious mononucleosis (IM) is probably increased in the presence of splenomegaly. The course of splenomegaly in IM has not been well documented. The purpose of this study was to describe the course of splenomegaly using ultrasonography and to determine if severity of symptoms and physical exam findings were associated with spleen size in patients with IM.

Thirty-seven subjects from 12-24 years of age diagnosed with IM were enrolled from primary care clinics in the community. Thirty-nine healthy controls were enrolled to establish confidence intervals for normal splenic measurements. At intake, subjects with IM were asked to rate the severity of 20 symptoms as either absent, mild, moderate, or severe. Each subject underwent a brief physical examination followed by 6 weekly splenic ultrasound measurements. A measurement related to volume, previously reported as the splenic volumetric index, was determined as follows: anteroposterior (cm) × longitudinal (cm) × transverse (cm)/27. Data analysis was performed using the Statistical Analysis System for descriptive statistics and one-way ANOVA.

All subjects with IM had splenomegaly (>95% confidence interval for healthy controls). The day of illness on which maximum splenic index was obtained was day 12.8 ± 6.0 (mean \pm S.D., range

3-31). Severity of symptoms and physical exam findings were not related to maximum splenic index except for the positive association between severity of periorbital swelling and maximum splenic index (p=.035). In addition, severity of symptoms and physical exam findings were not related to duration of splenic enlargement except for the positive association between severity of abdominal pain and duration of splenic enlargement (p=.034). Presence of a palpable spleen was not associated with splenic index (p=.09).

These data suggest that the course of splenomegaly in IM is highly variable. Severity of most symptoms and physical exam findings, including a palpable spleen, are not associated with either maximum spleen size or duration of splenic enlargement. Health providers cannot rely on the history or physical exam to determine when the spleen has returned to normal volume.

Young Adolescents' Experience, Knowledge, and Attitudes About Sexual Abuse

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This study examined the sexual abuse experience, knowledge, and attitudes of 7th and 8th graders participating in an educational program sponsored by the Massachusetts Child Assault Prevention Project. 446 students in several suburban public schools completed questionnaires before the four 1-hour sessions, and 316 students did so two weeks later. Sixteen percent of the girls and 15% of the boys reported a history of an unwanted sexual relationship. Before the program, 71% answered incorrectly concerning the prevalence of male victims of sexual abuse, 47% concerning female victims, and 66% concerning assault by strangers. There was no effect of previous abuse or gender on knowledge, but it was significantly improved by the program (F = 34.7, p<001).

Fifty-one percent agreed that a seductively dressed woman walking alone at night is asking to be raped, 59% agreed that a rape could be the victim's fault, and 25% agreed that incest could be an adolescent's fault, since s/he could have prevented it. Boys were significantly more likely to assign blame to the victim than girls, and mean attitude scores improved post program (p<.0001). Students were also asked in which of 11 situations on a date does a male have the right to a kiss or intercourse against the woman's consent (such as, "He spent money on her" or "He is so turned on he can't stop"). For individual situations, students' affirmative responses ranged from 4% to 73%. A composite score was created, with a higher score reflecting a more condoning attitude toward non-consensual sex. Boys had significantly higher mean scores for both kissing and intercourse, as did self-reported victims of sexual abuse. Scores for kissing were decreased significantly post program, especially for girls. Scores for intercourse were not significantly changed post program for either gender. Implications for prevention of victimization will be discussed.

Risk Factors for Suicide Attempts Among Native American Adolescents

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Rates of adolescent suicide in the U.S. are highest among Native Americans, but little is known about risk factors for suicide attempts in this population. To identify risk factors for selfreported suicide attempts by Native American adolescents, we analyzed the 1988 Indian Health Service Adolescent Health Survey.

This survey was administered anonymously to students in grades six to twelve on a large western Indian reservation (N=7254). The sample was 51% female and has a mean age of 14.7 years. Using univariate statistics and multivariate logistic regression, the responses of students reporting a previous suicide attempt were compared to others.

Ninety two percent of the students responded to the question: "Have you ever tried to kill yourself?" Nearly 15% (N=971) answered affirmatively with over half admitting to more than one attempt. Controlling for age, a logistic regression model revealed the following associations with suicide attempts: a history of mental health problems (OR=3.2; 95% CI=2.2-4.5), alienation from family and community (OR=3.2; 95% CI=2.2-4.4.4), having a friend who attempted suicide (OR=2.8; 95% CI=2.3-3.4), weekly consumption of hard liquor (OR=2.7; 95% CI=1.9-3.9), a family history of a suicide or attempt (OR=2.3; 95% CI=1.6-3.2), poor self-perception of health (OR=2.2; 95% CI=1.3-3.8), a history of physical abuse (OR=1.9; 95% CI=1.5-2.4), female gender (OR=1.7; 95% CI=1.4-2.0), and sexual abuse (OR=1.5; 95% CI=1.2-1.9).

This study demonstrates that adolescent suicide attempts in this population are strongly associated with alienation, poor health perceptions, child abuse, and exposure to suicide attempts among friends and family. Health and social service providers for Native American adolescents should consider the provision of special suicide prevention services to those clients with a history of these risk factors.

BEHAVIORAL PEDIATRICS

Hearing Loss and Attention Deficits: Etiological Considerations

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Despite the fact that attention deficits could place a child who is already struggling with hearing loss at double jeopardy for academic failure, there has been little research regarding the prevalence of attention problems in the hearing impaired and the role of hearing loss in the cause of attention deficits. We used questionnaires to study patterns of attention among deaf students.

Classroom teachers completed the ADD-H Comprehensive Teacher Rating Scale (ACTeRS) and Attention Section of the ANSER Questionnaire on 239 students (mean age 14.8 years, 55% male, mean IQ 103) at a residential school for the deaf. Their dormitory supervisors completed the 48-Item Conners Parent Rating Scale and the ANSER Questionnaire. Sixty four of the students had hereditary deafness, and 75 had a non-inherited physical cause (classified as neurologically at risk-NAR). Sixty eight percent were profoundly deaf and 69% had hearing aids.

Agreement between measures of attention was good (ACTeRS and Teacher ANSER-r=0.70; Conners Hyperactivity Index and Parent ANSER-r=0.73). Using accepted scoring criteria, attention deficits were not more prevalent among the deaf students overall compared to the general population. However significant differences were found when students were categorized by cause of deafness. Only 14% of students with hereditary deafness were rated as having attention problems on the ACTeRS in contrast to 39% of the NAR deaf students (p=.001). The NAR students similarly showed more problems than the hereditary deaf on the Conners Learning Factor (p=.01) and Impulsivity Factor (p=.02).

This study indicates that hearing loss per se is not associated with attention difficulties as measured by rating scales. However, non-inherited causes of deafness (which can be associated with

other neurologic damage) carry a higher risk of attention deficits, and etiology should be considered in educational planning for deaf students. These findings also raise broader questions about the impact of transient hearing loss on later functioning. While links have been reported between otitis media and subsequent attention deficits those findings might reflect the influence of other variables in addition to hearing loss alone.

Phobias Following Child Sexual Abuse

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Certain abuse characteristics, specifically, violence, related perpetrators, repetitive abuse, and penetration have been reported to result in greater psychological trauma among sexually abused children. The purpose of this study was to examine the phobias exhibited by children following sexual abuse and the association of phobias with these "traumatogenic" features of the

One to three weeks following sexual abuse disclosure, 495 children completed a questionnaire with their caretakers regarding recent onset of specific phobias. The children had a mean age of 8.6 years; 83% were female and 17% male. One hundred thirtythree children (26.9%) exhibited at least one new phobia including fear of: strangers/men (9.5%), being alone (8.9%), walking streets (7.3%), STDs/pregnancy (7.1%), leaving their house (6.5%), physical damage (5.3%), and darkness (5.1%). In addition, 21.4% of the children expressed fear of reprisal or fear of repeated victimization by the perpetrator. This fear was significantly more common in children who had phobias (Chi square, p<.0005), however 63 of these 106 children had exhibited no phobias. Fear of the perpetrator was more common when the abuse involved penetration (p<.001), but was not associated with other factors including the perpetrator's relationship, abuse duration, or the violence reported.

Phobias were more common when the child was related to perpetrator (p<.005) and perceived violence (p<.0005). Phobias were less commonly reported by white children (p<.01), but no significant relationship was found with age, gender, abuse duration, physical trauma, or penetration. Fear of physical damage was significantly associated with abuse perceived as violent (p<.005) or resulting in documented physical trauma (p<.005). Fears of STDs or pregnancy were more common among older

victims (p<.0001).

The emotional impact of sexual abuse in childhood is dependent on a number of factors. This study supports the concept that phobias are common following sexual abuse, and an increased frequency of reported fears was associated with the suggested "traumatogenic" factors of violence, related perpetrators, and penetration.

Stress and Adjustment in Boys With Hemophilia

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Children with chronic illness are at higher risk of psychological problems than other children. The mechanisms of increased risk are generally unknown. We studied 96 boys with hemophilia, ages 4-17, to determine whether stress affects their psychological adjustment.

Boys and parents each completed a daily diary for 6 months, describing daily perceptions of mood and stress, and a monthly questionnaire about major life events. Psychological adjustment was measured by the Child Behavior Checklist (CBCL) and the Personal and Roles Skills Test (PARS) both completed by parents; maternal self-esteem by the Tennessee Self-Concept Scale; and parenting style by a parenting rating scale (PRS). Higher CBCL behavior problems scores and lower PARS scores indicate less satisfactory psychological adjustment.

Subjects had CBCL behavior problem scores well above published norms (14.3% with scores above 70; norm, 2%) and lower social competence scores (9.1% less than 30; norm, 2%). Higher behavior problem scores on the CBCL and lower on the PARS were associated with younger age (p<0.03) and lower maternal self-esteem (p<0.01). Higher daily parent stress was associated with higher total behavior problems and internalizing scores (p<0.03) and lower PARS scores (p<0.05). Children who reported better moods had lower internalizing scores (p<0.03). Life events data were not associated with psychological status.

Mothers who scored high on a PRS factor related to their controlling and supervising the child's behavior had sons who had higher externalizing scores (p<0.02). Parents with high scores on a factor that indicated fostering responsibility in the child had sons with higher scores on the total social competence and

activities scales (p<0.001).

These findings confirm the psychological risk among boys with hemophilia and suggest that stress may exacerbate psychological problems. The PRS data suggest that attempts by mothers to restrict behaviors may lead to greater acting out (externalizing) behavior in their sons. Giving a son with hemophilia more responsibility for his actions and self-care may encourage participation in social activities.

Identification and Management of Psychosocial Problems in Pediatric Primary Care

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Community rates of psychosocial/developmental problems (PS/D) have been considerably higher than rates from pediatricians' practices. This discrepancy has led to the belief that pediatricians may not be identifying, treating, or referring children with PS/D problems. We suspected that the low rates of PS/D problems occurred because prior studies of physician practices emphasized psychiatric diagnoses, not PS/D morbidity. To test this hypothesis we investigated the diagnosis/management of PS/D issues in a stratified random sample of 19 out of 23 pediatric practices (83%) in the New Haven, CT area. We included 4 types of practices: solo (42%), group (37%), prepaid groups (11%), and neighborhood health centers (11%). We collected PS/D information from physicians using a 13-category checklist based on a WHOsponsored primary care classification system.

Of 2006 children 4-8 yrs. visiting these practices, 1886 children and their families (94%) participated. At entry, 52% were 4-5 yrs., 50% were male, 80% were white, 73% had married parents living together, and 48% were first born. 33% of the children were

visiting for preventive care; 59% for acute care.

Pediatricians identified 520 children (27.5%) with \geq 1 PS/D problem, for a total of 921 current problems. Pediatricians most often identified problem areas as: family (7.5%) (e.g., divorce), behavior (6%) (e.g., bedwetting), and cognitive/language (5.9%) (e.g., learning disability). Problems least often identified were: peer activity (1.5%) (e.g., social isolation) and thought (.2%) (e.g., delusions). 33% of problems were classified as mod./sev., 31% as mild ≥12 mo. duration and 18% as mild ≤12 mo. duration. Pediatricians were more likely to identify problems if children were: male (RR = 1.4), well known to the doctor (RR = 1.5), and visiting for well-child care (RR = 2.0). Problem management was identified for 911/921 problems. In 46%, problems were noted/not treated in 47%, physicians intervened; and in 6%, physicians referred. Moderate/severe problems were more often referred

(14%) than mild, short problems (5%).

These data suggest that when using a classification system appropriate for primary care, community pediatricians identify problems in many (27.5%) children. Physicians can serve as effective identifiers and managers of PS/D problems.

Factors Influencing Frequent Pediatric Emergency Room Use

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The dramatic increase in emergency room (ER) utilization during the past 2 decades among low SES inner-city populations is costly in staff and facilities, and does not promote continuity of care. We studied factors associated with the frequent use of a university pediatric ER during an 8 week study period. Of the 4521 ER visits recorded, 705 consenting primary caregivers (CG) were surveyed by trained interviewers before the child was seen by a physician in the ER. The study population consisted of innercity, CG of children (black = 98%), ages <1 mo-19.8 yrs. These CG were primarily unmarried (84.2%) females (96.0%) not employed outside the home (73.6%), with education ranging from 4 to 18 years. To gain an index of ER utilization, interviewers queried the CG as to how many times they had brought the index child to any ER within the past year. For a substantial number (n=265), the interview contact was their first ER visit, but (62.4%) reported having brought the child to an ER more than once in the past year. Multiple regression analysis revealed 5 factors significantly related to frequent ER use: the CG's perception of the child's health as poor (p=.016); having a nonparent care for the child during the day (p=.008); whether the child had been hospitalized since being discharged after delivery (p=.002); the extent to which the CG had worried about the child's health in the past year or since birth (p=.0001); and whether the child had multiple medical problems (p=.0001). Several other factors such as the child's sex, extended stay in hospital after delivery, night vs. day ER use, having nonparent care for child at night, having a primary care doctor, length of residence at current address, having more than one adult in the home, the child's father and CG's employment status, education, marital status, self-rated health, or their use of ER for themselves, were unrelated to frequency of ER use by the child. We conclude that while frequent ER use may be deemed inappropriate from medical-model or cost-efficiency perspectives, CG appear to act primarily out of concern about their children's health. The relationship of frequent ER use to the care of the child by a nonparent during the day, coupled with a high unemployment rate among CG is interesting and needs further exploration.

EPIDEMIOLOGY AND PREVENTIVE PEDIATRICS

Unsuspected Cocaine Exposure in Young Children

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Cocaine use has increased dramatically over the past decade. There is little information about passive exposure to cocaine among children. The purpose of this study is to determine the prevalence of cocaine exposure in patients with clinically unsuspected signs and/or symptoms of the exposure.

Parents and their children (2 weeks to 5 years of age) seeking care in the pediatric emergency department were asked to partic-

ipate anonymously and with informed consent by providing urine which was assayed for cocaine metabolite (n=443). Eighteen parents refused to partic pate. Of the remaining 425, 250 children (59%) provided urine prior to discharge from the ER. The mean age of the children was Ξ months (range 2 weeks to 5 years with 40% less than 1 year), 59% were male and 53% black. Six of the 250 urines (2.4%) were positive for benzoylecgonine (all 6 positive by EMIT, 1 confirmed by gas chromatography/mass spectrometry, 1 confirmed by thin layer chromatography and 4 reconfirmed by repeat EMIT). The characteristics of the infants are as follows.

Age	Complaint		Vitals		Diagnosis
1m	Cough	T:98	P:120	RR:40	Pneumonia
4m	Wheezing	T:10C.3	P:120	RR:32	Reactive Airway Dis.
		T:99.3	P:132	RR:32	Otitis Media
9m	Fever	T:10£.7	P:168	RR:52	Bronchiolitis
22m	Fever	T:102.7	P:160	RR:36	R/O Sepsis
19m	Trauma	T:99.3	P:140	RR:36	Laceration

Possible exposure rou-es include (1) breast feeding (one month old infant), (2) intentional administration, (3) accidental ingestion, and (4) passive inhalation of crack vapors in children that are in close proximity to aerosolized cocaine.

We conclude that infents and toddlers are being exposed to cocaine and that this occurs in a clinically unsuspected population. The clinical and public health implications of these findings, which are unknown at this time, will be very important to elucidate by subsequent surveillance and study.

Factors Associated With Delay in Diagnosis of Childhood Amblyopia

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Preventing permanent visual impairment from amblyopia is an important goal of pediatric vision screening. However, previous research has shown that many children (including those with good access to medical care) are not diagnosed until the child is too old to benefit maximally from treatment. The purpose of this study was to identify factors associated with late detection of childhood amblyopia, so as to identify those that might be amenable to intervention.

161 children with amblyopia selected from the practice of a pediatric ophthalmologist participated in a case control study in which children diagnos∋d after age 5 years (cases, n=75) were compared to those diagnosed before 5 years of age (controls, n=86). Data were collected from the ophthalmologist's medical records, an interview with the parents, and a survey of vision screening practices of the children's pediatricians. A number of statistically significant differences (p<.05) were identified between the groups. Children diagnosed early more often had the following characteristics: a positive family history of strabismus, greater degrees of strabismus, higher maternal educational level, greater parental suspicion that an eye problem existed, and an increased chance that the parents requested the eye exam that led to the diagnosis. The parents of the children diagnosed late expressed less concern about the seriousness of amblyopia, but were more likely to report that their children had suffered adverse consequences of amblycpia. Children diagnosed early were more often detected by their primary health care provider, although overall only 25% of the children's vision problems were first identified by their pediatrician. Pediatricians of the children diagnosed early more often reported compliance with the AAP guidelines for vision screening in infancy and referral for vision problems.

Late detection of amyblyopia appears to be a multifactorial problem involving characteristics of the child's visual problem, the family and the medical system. Consideration of these factors should help to improve early detection of childhood amblyopia.

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Hemoglobin Norms for Minority Inner City Infants

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Hemoglobin (HGB) reference values for infants have been derived primarily from sampling of Caucasian populations; whether these values apply to minority inner city infants is not known. To establish normative data for the latter population groups, we conducted a cross-sectional survey of 705 unselected Black and Hispanic healthy infants between the ages of 5 and 7 months (mean age 6.3 mo) seen for well-baby visits at a hospital based faculty practice in New York City. Most of the infants received Medicaid (80%) and participated in the WIC program (77%) which requires screening for anemia every 6 months. In our study, sampling was venous; HGB and mean corpuscular volume (MCV) were measured with the Coulter counter, erythrocyte porphyrins (EP) by the Piomelli method and ferritin (FERR) by Ramco kit. Infants with abnormal (51) or unknown (62) HGB electrophoresis and possible thalassemia trait (MCV <70 n=22) were excluded from the analysis. Data from premature infants and of those with FERR values <15 were included as their mean HGB was not lower than the rest of the sample. There were no significant differences for values obtained at 5, 6 and 7 months of age. The results are shown in the table below.

		HG: (gm/	_	MC (fl		EP (µg/dl)	FERR (ng/ml)
	'n	mean	SD	mean	SD	mean	mean
All	570	11.5	.90	79.0	3.9	30	32
Female	298	11.6	.94	79.4	3.7	29	37
Male	272	11.5	.84	78.6	4.0	31	28
Black	174	11.5	.89	78.4	4.0	. 27	32
Hispanic	396	11.6	.90	79.3	3.8	. 31	33

The HGB values approximate a normal distribution. The HGB value at the 5th percentile for these inner city Black and Hispanic infants is 10.2 gm/dl, clearly lower than the commonly accepted value of 11.0 derived primarily from Caucasian infants. These data, together with our previous report showing that additional iron did not increase HGB, may be useful in interpreting laboratory results and in preventing unnecessary therapy in these infant populations.

Socioeconomic Status (SES) and Survival in Childhood Acute Lymphoblastic Leukemia (ALL)

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While more effective treatment regimens have led to increased survival in childhood ALL over the last two decades, the role of non-disease, non-treatment factors is not well understood. Several authors have reported 2-fold differences in survival and 3-fold differences in mortality from ALL between children from upper and lower social classes. Although mediators of this effect might have included differences in biologic subtype (covariates), nutrition, and variations in or compliance with treatment related to SES, information on these potential predictors of survival have not been studied. We collected relapse, survival, socioeconomic, biologic covariate, nutritional, and treatment data on 125 children presenting with ALL between 1976 and 1985. Complete covariate information on white blood cell count (WBC), age, sex, immunophenotype (IPT), French-American-British (FAB) classification, treatment and body mass index was available for a subset of 81 of the children. SES was measured by individual head of household occupation and/or a neighborhood-based measure of median household income.

To the best of our knowledge, all children in the Canadian health

care context receive full treatment for malignancy; in our study. SES groups were confirmed retrospectively to have been assigned to appropriate risk-specific treatment protocols. Further, body mass index (BMI) at diagnosis and weight loss in the first month of therapy were not associated with SES. Finally, cox regression models with time to relapse or death as outcome, and age, sex, WBC. IPT, and FAB as independent variables were significant at P = .017 and .007 levels respectively. SES was strongly associated with IPT (P = .01) and to a lesser extent with FAB (P = .16), but not with survival.

We thus could not detect an independent effect of SES on survival or relapse in children with ALL. The observed associations between SES and biologic tumor markers however, suggest that previous reports of such effects may be explained by factors affecting the distribution of biologic subtype of childhood ALL along social class lines. Further, equal access to medical care in Canada may have reduced or eliminated the potential impact of

GENERAL PEDIATRICS

Black Clouds: Do Some Residents Really Work Harder?

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Some pediatric residents become known for their "Black Clouds," i.e. they are believed to consistently have more difficult nights on call. We collected data about on-call experiences (CALLs) for 353 days (1355 CALLs) in 1984-5 in order to determine the degree to which CALLs vary. Every PL1 (N=19) reported the following data the morning after each CALL: hours of sleep, number of admissions, deaths, transfers to ICU, total patients, delivery room trips, and subjective assessment of workload. Services covered included 3 general medical wards and 2 NICU's.

There were 2.6 ± 2.1 (mean ± SD) admissions per CALL (range 0-10), and residents averaged 3.1 ± 2.0 hours of sleep. When in the NICU, residents averaged 4.3 ± 2.3 trips to the delivery room (range 0-11). Workload was highly correlated with sleep (r = -0.75), admissions (r = 0.5), and patients (r = 0.44). Workload varied with ward (p<0.001, ANOVA); the wards perceived to have the heaviest workloads included one with many oncology patients, and the NICU's. Deaths were infrequent, and overall did not predict workload. However, workload was greater when a death occurred (p < 0.001).

Significant differences between PL1's were observed for workload and sleep (p<0.001, ANOVA) but not for admissions or number of patients. Thus, some PL1's did sleep less and perceived greater workloads than their colleagues, but the differences did not simply result from more admissions or patients. Although there were high correlations between workload and admissions. and sleep and admissions for some PL1's, this was not true for all residents.

Conclusions: 1) differences between residents in workload and sleep are self-imposed (i.e. black clouds come from within); and 2) these differences may affect resident satisfaction and performance, and should be considered in program design and resident evaluation.

Predicting Students' Exam Results From Their Pediatric Clerkship Performance

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Medical students' clinical experiences on a pediatric clerkship are usually very focused yet uniquely diverse among class members. Final evaluations are often a compilation of students' clinical performance and cognitive knowledge on a standardized written examination. In order to determine the most predictive factors of a student's performance on the National Board of Medical Examiners (NBME) pediatric shelf exam, the authors studied the following parameters for 150 third year GWU medical students after their eight week clerkship at CNMC in 1987-88: 1) number of patients seen as determined by student logs; 2) NBME pediatric shelf exam; 3) formal written and oral case presentation to peers; 4) clinical performance. The authors hypothesized that while the clinically-related experiences (number of patients seen, case presentation, and clinical performance) of students' training would be correlated, these would not be correlated with NBME scores. By applying a multiple regression model, we determined which of the students' performance parameters were most predictive of their NBME score.

Surprisingly, results revealed poor correlation between clinical performance and case presentation grades (0.1629). Only one variable, clinical performance, entered the regression model. No other variable provided for significant prediction of exam score, and clinical performance accounted for only 3% of overall variance. Also unexpected, the number of patients seen during the rotation was not a significant predictor of exam performance, nor was the case presentation, which reflects a student's organizational & synthesizing skills. Each of the performance measures studied appear unrelated to one another, since all simple correlations were non-significant.

Our results revealed that performance on an objective cognitive exam cannot be predicted by clinical parameters. We conclude that singular reliance or emphasis on any one of the parameters studied to evaluate a student's performance on a pediatric clerkship would be ill-advised.

Effectiveness of Computer Generated Appointment Reminders

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Published studies of appointment reminders in general pediatric practices have been exclusively among lower socioeconomic populations. We studied the effect of computer-generated reminder cards in a patient population similar to many private pediatric practices. A randomized trial of reminder cards was conducted among 859 appointments over a 6 month period in a model primary care center with a high level of continuity. Cards were generated automatically by a personal computer using a previously described automated patient-physician scheduling system (AJDC 143:1333) and were mailed I week before the scheduled appointment. Control patients did not receive cards.

Study patients were 70% middle or upper socioeconomic status. The 46% reduction of the overall no-show rate from 18.7% to 10.1% was highly significant (p<.001). The magnitude of reduction of no-shows was similar for appointments scheduled more than 14 days prior to the appointment time (43%) as well as those scheduled more recently (51%). Equivalent results were seen with well checks (47%) as well as other visits (45%). Reminders mailed to faculty patients resulted in similar reductions in no-shows (55%) as those mailed to resident patients (42%). Both lower and upper/middle socioeconomic groups demonstrated similar results. The mailed cards cost \$.211 each, including costs of materials, personnel time, and postage. In our practice they generated an estimated \$9.83 in increased net practice income for each \$1 spent and thus were highly cost effective.

Although the income generated for each no-show converted to a kept appointment would be different in other practices, the cost per card using this system should be similar. We estimate that many practices should find these computer-generated reminders to be cost effective if they reduce the no-show rates by only 15-20% and the current rates are greater than 4-7%.

Abdominal X-Rays, Intussusception, and the E.D.

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Intussusception requires early diagnosis and barium enema. E.D. physicians often order plain abdominal x-rays prior to obtaining a barium enema. Large series report up to 90% with abnormal findings, yet the sensitivity and specificity of abdominal x-rays read by non-radiobgists without knowledge of outcome has never been studied.

We designed a retrospective study simulating a prospective clinical trial to examine this question. Forty-two consecutive patients, ages 3 to 36 months, diagnosed with intussusception were studied with two control groups matched for age and sex. The clinical control group was 42 patients with clinical suspicion of intussusception, who cid not have disease. The normal controls were 42 patients with a final x-ray report of "normal". The 126 flat and upright x-rays were placed in random sequence and read by 6 full time pediatric E.D. physicians. The clinicians were asked if they would order a BE based on x-ray findings. The results are as follows:

Study Group	Findings	Overall	Range	Kappa
Disease Group	Clinical Sensitivity	81%	71-93%	0.31
Clinical Control	Clinical Specificity	58%	48-69%	0.49
Normal Control	Control Specificity	83%	74-86%	0.09

The control specificity reflects the tendency to overread. There was significant difference between clinical and control specificities (p<.0001). All Kappa statistics were significantly different from 0 (p<.05).

Large series have shown sensitivities for the classic trial of abdominal pain, vomiting, and bloody stool to be 75-90%, 60-80%, and 20-55% respectively. With a sensitivity of 81% and a specificity of 58%, abdominal films read by experienced non-radiology clinicians offer another useful tool in the management of this illness.

Cost Effectiveness of Erythromycin Versus Mupirocin for the Treatment of Impetigo in Children

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Impetigo treatment has evolved with the advent of new antimicrobial agents, the shift of etiologic agents, and the emergence of resistant bacteria. A new topical antibiotic, mupirocin (M), has been found to be as effective as oral erythromycin (E), but is felt to be more costly. This clinical trial assessed the relative cost-effectiveness of these drugs.

Subjects drawn from the ER and the continuity clinic of an urban teaching hospita were randomly assigned to receive 10 days of either E (n=46 or M (n=47). Treatment groups did not differ significantly by ratient or disease characteristics (ages 3 mos-16 yrs, mean 4.4 yrs; mean wt 19.9 kg; 89% black; 63% male; 41% household income <\$10,000; mean pre-enrollment duration of impetigo 7.7 days; 69% nonbullous, 17% bullous, 14% mixed).

Lesion morphology/extent and history were documented at presentation. Patient cozts (number of visits, amount of medication and transportation expenses) and effects (clinical and bacteriologic response, time to resolution, side effect frequency/severity, ease of drug administration, change in daily activity, satisfaction and compliance) were measured through structured interviews during and at the end of therapy.

Cost per case differed significantly by group (M=\$60.70; E=\$54.35; p<.04), due chiefly to extra visits (12%) and/or medication changes (7%) needed by those treated with M. There was no difference in the effectiveness of E or M (100% clinical cure/improve; 5% bacteriologic failure; mean days to resolution=8.6). The likelihood of side effects (E=43%, M=22%) approached

significance (p<.07); those treated with E were more likely to be willing to pay more for a different medicine in order to avoid the side effects experienced (p<.05). Other differences in effects did not reach statistical significance, but might be clinically important (mean schooldays lost E=2.7, M=1.2; mean parent workdays lost E=.5, M=.2; noncompliance E=2%, M=10%). Parent satisfaction did not differ by group. We conclude that type of medication prescribed can be based on parental preference because the increased cost of M is probably offset by the increased side effects and number of schooldays and workdays lost with E.

GENERAL PLENARY SESSION

Cost Analysis of a Pre-Paid, Capitated, Managed-Care Program for Medicaid Children

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Office based primary care pediatricians (PCP's) often do not participate in Medicaid because of low remuneration. Only 15% of PCP's in Erie County, N.Y. (greater Buffalo) participate in Medicaid. The Children's Medicaid Program (CMP) is a State and County sponsored, ongoing (5/1/87-4/30/91) demonstration project in case-managed care for children and is being implemented by PCP's at The Children's Hospital of Buffalo. The goal is to provide a model for office-based, managed health care for Medicaid children at competitive rates in order to attract more PCP's to the Medicaid market. Such care should decrease costly utilization of clinics, emergency rooms (ER), and specialists and improve quality, access, and continuity.

Cost data from the first 24 months were analyzed. CMP PCP's received a monthly fee (ranging from \$8.34 to \$42.47 and varying by age and sex) to provide primary care to a group of Medicaideligible children. These children (aged 0 to 20 years) were recruited at the time of Medicaid recertification. Referred services (e.g. pharmacy, inpatient hospital, lab) with some exceptions (ER, dental) required PCP approval. CMP costs were compared to costs for a similar group of Erie Co. Medicaid children using data from New York's computerized payment system. After 24 months, there were 978 CMP children and 41,501 in the comparison group. Costs per enrollee per month were as follows:

	Regular Medicaid	СМР	р
Primary Care	\$ 8.94	\$14.91	<.001
Referred Services	22.76	7.54	<.001
ER	4.62	2.76	<.001
Total	\$36.32	\$25.21	<.001

The increase in primary care costs was more than offset by the decrease in the costs of referred services and ER. Such managed care programs can significantly increase remuneration to PCP's, improve access, and decrease total costs.

Readability of Childhood Immunization Consent Forms

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"Important Information Statements" produced by the Center for Disease Control are widely used throughout the U.S. in obtaining caretakers' informed consent for routine childhood immunizations. It is very important that these forms be readable, yet in our experience, the caretakers of our patients demonstrate

significant difficulty in reading them. The objective of this study was to compare the reading level of the consent forms with the reading level capabilities of the caretakers of our clinic population.

One hundred and fifty consecutive caretakers meeting inclusion criteria were tested for reading level. Criteria included payment coverage by Medical Assistance (or equivalent insurance), and English as their primary language. The reading level of each subject was assessed using the Reading Level II portion of the Wide Range Achievement Test. The reading level required for the "Important Information Statements" was assessed using the Fry Readability Graph. The participation rate was 95.5%. The reading grade levels of the caretakers ranged from grades 2.9-13.3, with a mean grade level of 7.07 (95% confidence intervals 6.70-7.44), and an S.D. of 0.19. The reading levels required for the Statements and % of caretakers who met or exceeded those levels are shown below:

	DTP	OPV	MMR	Haemophilus B conjugate
Reading level of consent form	12.3	15.3	10.3	15.3
% of caretakers attaining level	2%	0%	12%	0%

These results indicate that a vast majority of caretakers in our clinic population have reading levels insufficient to cope with even the simplest of the "Important Information Statements." This presents a significant impediment to obtaining a valid informed consent. The CDC's new Statements, currently in draft form, should be scrutinized carefully for reading level, and thoroughly pre-tested to assure maximum readability while continuing to provide adequate information for medical and legal purposes.

Efficacy of Nebulized Metaproterenol in Improving Symptoms of Children With RSV Bronchiolitis

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The role of inhaled beta adrenergic bronchodilators in treating infants with a first episode of bronchiolitis associated with RSV infection is controversial. To determine whether nebulized metaproterenol is effective in this circumstance, we evaluated 21 infants with cocumented RSV infection who participated in a double-blind, randomized, placebo controlled trial. The infants had a mean age of 10.1 months; all were full term, none were chronically ill, and all presented as outpatients with a first episode of acute wheezing.

The infants received nebulized metaproterenol sulfate, either as an initial treatment or after a control treatment with normal saline. At baseline and 20 minutes after each treatment, an assessment was made which included heart rate (hr), respiratory rate (rr), oxygen saturation by pulse oximetry, and a standardized clinical index (respiratory distress index, RDI) based on 3 critical variables: wheezing, retractions and flaring.

Infants who received placebo as initial therapy had no significant differences from baseline in any of the assessment measures. After metaproterenol, infants demonstrated an increase in hr (151 \pm 18E vs 156 \pm 4, p \leq 0.05), a decrease in rr (53 \pm 2 vs 46 \pm 2, p \leq 0.05) and improvement (lower scores) on RDI (15 \pm 1 vs 9 \pm 1, p \leq 0.01). There were no differences in oxygen saturation (95.4 \pm .6% vs 95.9 \pm .7) When strict criteria, developed prior to the analysis, were applied to define responders to metaproterenol, 10/21 patients (48%) had both a decrease in rr \geq 20% and improvement in RDI of \geq 50% compared to premedication values. When either criterion of rr or RDI alone was applied, an additional 4/21 (19%) were responders.

These data indicate that nebulized metaproterenol is effective in improving the symptoms of children with RSV bronchiolitis.

The Risks and Benefits of Acetaminophen Antipyresis in Young Children With Fever of Presumed Viral Origin

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Animal experiments and in vitro studies of human immune function suggest that fever may be of adaptive value in combatting infection. Moreover, the "modern" emphasis on treating children with fever rests on undocumented, anecdotal claims of improved comfort and behavior. To provide an objective assessment of clinically relevant risks and benefits, we carried out a randomized, double-blind, placebo-controlled trial of 162 children 6 mo-6 yrs who presented to a private group pediatric practice or a children's hospital emergency room with documented fever (T≥38° C per rectum) of acute (≤4 days) onset and without evident or subsequent bacterial focus of infection. Parents were asked to administer acetaminophen (AM) 10-15 mg/kg or placebo (PL) in equivalent volume every 4 hours as needed for fever and to avoid bathing, sponging, or other pharmacologic agents. Temperature and symptom diaries were used to assess duration of fever and other illnessassociated symptoms. Changes in child comfort and behavior were examined using a pretested, 5-point Likert-type questionnaire completed by parents 1-2 hours after each dose of study medication.

Randomization resulted in AM (n=90) and PL (n=72) groups similar in mean age (25.1 vs 26.8 mo), temperature at presentation (38.9 vs 38.8° C), prior duration of illness (42.0 vs 44.6 hrs), and Green SES score (66.6 vs 65.2). No significant differences were detected in mean duration of subsequent fever (31.2 vs 37.1 hr. P=.340) or other symptoms (76.8 vs 73.3 hr, P=.761). On the other hand, children treated with AM were rated by their parents as having slightly greater improvement in activity (0.6 vs 0, P=.005) and alertness (0.6 vs 0.1, P=.012). Differences in mood, comfort, and appetite were in the same direction but did not achieve statistical significance. That improvements in behavior and comfort with AM were not impressive is also underscored by the low success rate of parents' "guess" (after completing the trial) as to which medication their child had been assigned: 38.9% for AM and 51.4% for PL. Our data thus suggest that the clinically relevant risks and benefits of acetaminophen antipyresis have been overblown and provide a more rational basis for therapeutic decision making in the young febrile child.

Lower Respiratory Illness in Infants and Low Socioeconomic Status

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Infants from low socioeconomic status (SES) families have been said to suffer higher rates of lower respiratory illness (LRI), but this assertion has not been carefully examined. We studied the frequency and determinants of LRI in infants of different SES by analyzing data from a community-based cohort study of respiratory illness during the first year of life in healthy newborns in North Carolina. The incidence of acute LRI was determined by telephone calls at two week intervals and the prevalence of chronic lower respiratory symptoms by questionnaire at 7 and 12 months. Demographic, environmental and psychosocial risk factors, and urine cotinine (a marker of smoke absorption) were measured during home visits at 2 weeks, 7 months and 12 months. SES was classified according to the educational achievement of the head of household.

The 396 infants studied were 20% low SES, 31% middle SES and 49% high SES. The incidence of LRI (episodes/child-year)

was slightly higher in the low and middle SES groups: low 2.0, middle 2.0, high 1.4. However, the prevalence of chronic respiratory symptoms at one year of age was much higher in low SES infants: low 39%, middle 24%, high 14% (RR=2.9 low vs. high, 95% CI 1.9, 4.5). The risk of chronic respiratory symptoms was reduced after controlling (by logistic regression) for household crowding, exposure to tobacco smoke, and type of feeding, but not after controlling for family history of respiratory illness or allergy, woodburning stoves or gas cooking fuel. Enrollment in day care was associated with an increased risk of chronic symptoms among high SES infants (RR=2.2) but not in low SES infants.

Low SES infants are at increased risk of chronic respiratory symptoms. This risk can be partly attributed to environmental exposures, most of which could be changed.

Do Retinal Hemorrhages Occur With Accidental Head Trauma in Young Children?

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The finding of retinal hemorrhages in a young, head injured child with a history of accidental trauma often raises the question of inflicted injury. Because it is unclear whether retinal hemorrhages occur as a result of common accidents, we conducted a prospective evaluation of 50 children ≤24 months old who presented to the emergency department with well documented acute head trauma without the suspicion of maltreatment. A pediatrician or neurosurgeon recorded historical and biomechanical factors related to the injury on a standardized form. Head trauma was evaluated with detailed neurologic exam, skull x-rays, and/or CT scans. An ophthalmologist performed a standard retinal exam within 24 hours of injury.

Patients studied had a mean age of 11.4 months, 54% were male, 56% were white, and 68% were of low SES. The mechanism of injury included 26 falls down stairs (52%) (19 in walkers), 15 falls from heights ≤4 feet (30%), 4 falls from ≥10 feet (8%), 2 impacts by moving objects (4%), and 3 unrestrained motor vehicle accidents (6%). Thirty children (60%) were hospitalized: 10 with abnormal neurologic exams alone, 14 with uncomplicated skull fractures, and 6 with intracranial injuries. Two of the intracranial injuries were intracerebral hemorrhages (from motor vehicle accidents), 2 were epidural hemorrhages (from a fall ≤4 feet and a fall down steps) and 2 were subarachnoid hemorrhages (from falls ≤4 feet). Except for motor vehicle accidents, the mechanism of injury did not predict the degree of severity of neurologic injury. All children recovered rapidly without neurologic sequelae, although both children with intracerebral hemorrhages remained lethargic for several days. Retinal hemorrhages were not found in any of the 50

The data from this preliminary prospective study indicate that retinal hemorrhages are not regularly found in young children who sustain mild to moderate head trauma as a result of common accidental injury.

Unscheduled Return Visits to a Pediatric Emergency Department: A Prospective Study

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Children making unscheduled return visits (UR) to emergency departments are problematic because they may reflect deficiencies in patient care and/or communication between physician and family. We undertook a prospective study to compare UR's to a

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control group not making unscheduled return visits (C) in order to analyze the factors associated with UR's with the eventual goal of reducing the number of UR's.

During 3 consecutive months (12-'88 to 2-'89), all UR's within 48 hours of the initial ED visit were identified by computer log and daily ED record review. For each eligible UR, 1 or 2 controls (C) were selected randomly, depending on the time of the return visit. The charts of all UR's and C's were reviewed. A telephone interview regarding patient satisfaction, compliance, understanding, and socioeconomic status (SES) was performed for all available patients.

There were 221 UR's (2.6% of the 8579 patient visits) during the study period, and 355 C's were selected. Telephone interviews were completed for 126 (57%) of UR's and 184 (52%) of C's. There were no statistical differences between UR and C in sex, age, race, language, SES, or proportion having a primary physician. There was a difference between the UR and C in time of arrival, with 15% of UR and only 8% of C presenting between midnight and 0800 hours (p<.008).

The 5 most frequent diagnoses in descending order for UR were asthma, gastroenteritis, otitis media, viral syndrome, and bronchiolitis. For C they were otitis media, URI, asthma, viral syndrome, and gastroenteritis. The diagnosis was changed in 49% of UR at the time of the return visit. Seven UR's required emergency procedures, including 2 intubations, 2 bronchoscopies, 2 laparotomies, and 1 shunt revision. As compared to C, UR spent longer in the ED, had more lab tests ordered, and more medications prescribed (p<.002). By telephone interview, significantly more UR's than C's reported deficiencies in physician understanding and addressing of parental concerns (34% v 11%, p=.001). In 7 of 12 patient satisfaction questions, UR responses indicated less satisfaction than C (p<.007). When asthmatics were removed from analysis, all the differences between UR and C remained except for the number of medications prescribed.

We conclude: 1) Physician assessment of parental understanding and satisfaction during the discharge discussion may require more careful attention. 2) The fact that more UR than C patients were seen overnight when there was no supervising attending physician available suggests the importance of senior physicians in the ED at all times. 3) There were no "high-risk" diagnoses. The leading diagnoses in both groups were routine and medical.

The Denver II: Revision and Restandardization of the DDST

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The Denver Developmental Screening Test (DDST), originally standardized in 1967, has undergone major revision and restandardization. A pool of 336 potential items was created and criteria for the administration and interpretation of each item were developed. The items were standardized upon two samples: 1) Denver County (N=1039) and 2) Colorado non-Denver County (N=1057). The Denver County group was subdivided into three ethnic groups. The Colorado non-Denver County group was subdivided into three residence categories (rural, suburban, urban). All of the groups were then further subdivided on the basis of maternal education and age of children.

Each item was analyzed via regression analysis to determine age at which 25, 50, 75, and 90% of children in each subgroup could perform the item. A "goodness of fit" test was applied to determine the accuracy of the curves. Curves not meeting the "goodness of fit" test were further revised until they met the standard. Tester-observer and test-retest reliability were determined for each item.

The final selection of 125 items was made on the basis of eight criteria, resulting in an 86% increase in language items, the addition of two items on speech intelligibility, and a 16% decrease

in the number of report items.

The 125 items are displayed on a test form which has an age scale corresponding to AAP-recommended health maintenance visits. The test form also includes a behavior rating scale.

The Denver II Screening Manual, test form, and proficiency test have undergone field testing in diverse parts of the U.S. A Technical Manual contains norms of subgroups having significantly different ages from the overall group norms at which 90% of children pass various items.

Endotracheal Tube Selection in Children: A Comparison of Four Methods

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Selecting an appropriately sized endotracheal tube (ETT) for a child in an emergency is both important and difficult. Several methods for ETT sizing have been cited in texts but few properly studied. The method of selecting an ETT for a child by direct comparison to the fifth finger is widely taught and is included in the ACLS and PALS courses, yet no American or European studies have examined this method of ETT selection. We compared four methods of determining proper ETT size in 218 children less than 10 years of age undergoing elective surgery requiring intubation. These methods included: direct comparison with the fifth finger and with the fifth fingernail, ring sizing with a precut card and estimation using a formula (age in years + 16)/4. In infants a 3.5 tube was predicted for age one to six months and a 4.0 tube for age between six months and one year. The actual sized ETT used in the operating room was recorded as was the "leak" around the tube. An appropriate sized tube was determined by a leak >5 cm H₂O and <40 cm H₂O. We found that direct comparison using the fifth finger and the precut card predicted an ETT one to three mm (internal diameter) larger than that used in the operating room in 192 patients (88%) and 186 patients (85%), respectively. Conversely, direct comparison with the small fingernail predicted an ETT within 0.5 mm (internal diameter) of that actually used in the operating room in 176 (81%) patients and use of the formula in 122 (56%) patients. These findings were equally consistent within all age groups. Our data indicate that neither fifth firger width nor formula estimation accurately predict ETT size in most children, and that a more accurate estimation can be made using direct comparison to the fifth fingernail. We suggest that the recommendations in ACLS and other such courses be amended to reflect these data.

Is a Chest X-ray Necessary in the Evaluation of Every Febrile Infant Less Than Eight Weeks of Age?

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Most physicians continue to order a chest x-ray as part of the routine evaluation of very young febrile infants to rule out a clinically silent pneumonia. However, routine chest radiography has a number of drawbacks, including exposure to radiation. This study examined the extent to which an abnormal chest x-ray occurs in a population of febrile infants ≤8 weeks of age in the absence of respiratory signs and symptoms (RS).

The sample consisted of 237 infants who presented over a 3 year period with T≥100.4°F, all of whom had a chest x-ray (CXR). The houseofficer recorded the presence of RS including rhinorrhea, tachypnea, cough, rales, wheezes, retractions, and rhonchi. All infants were admitted to the hospital. Each CXR was independently reviewed according to predetermined criteria by a senior radiology resident and an attending pediatric radiologist; both

observers were blind to the infants' RS. The CXR was judged abnormal if either 1 or both observers rated it so. If abnormal, the CXR was assigned to 1 or more of the following categories: hyperinflation, diffuse process, localized peripheral cpacity (infiltrate), or pleural effusion. These CXR interpretations were com-

pared to the presence of RS.

Interobserver agreement was 94%. Of the 237 cases, only 27 CXR's (11%) were identified as abnormal, including 14 where there was disagreement as to the presence of an abnormality. There were no cases of occult pneumonia. Twenty five of 82 infants (30%) with any RS had an abnormal CXR, while only 2 of 155 asymptomatic infants did (1.3%) (p<.0001). In both asymptomatic cases, the CXR was read as normal by one radiologist and as mild diffuse by the other, and medical management was not affected by the CXR reading. These findings suggest that febrile young infants with no respiratory signs or symptoms are unlikely to have an abnormal CXR.

Use of Randomized Response to Estimate Substance Use in a School-Based Clinic Population

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Health-care providers in school-based clinics have been struck by the low rates of substance use reported by their patients. We used a statistical method, Randomized Response (Science 236:382, 1987), to help determine whether these rates are accurate. Randomized Response involves the use of a random event, such as flipping a coin, throwing dice, or picking different colored marbles from a bag, to ensure confidentiality to respondents answering sensitive or controversial questions. A researcher interviewed 206 students in the Far Rockaway High School Clinic during May/ June 1989, asking questions about substance use and sexual activity during the past 3 months. Subjects were instructed to pull a marble out of a bag containing green and pink marbles before answering each question, and to answer the question honestly if the marble was green or "yes" if the marble was pink. They were told not to let the researcher see the marble so she would not know the actual answer to any question. The 206 students were 52% female, 48% male; 75% black, 13% Hispanic; 54% grades 9-10, 46% grades 11-12. Prevalence rates calculated from the answers given by Randomized Response (with 95% confidence intervals) were compared for the 131 students who had answered the same questions on an intake questionnaire earlier the same academic year:

	Questionnaire Response	Randomized Response
cigarette use	5% (1-9%)	25% (14-37%)
alcohol use	20% (13-27%)	36% (24-47%)
marijuana use	2% (1-3%)	0% (0-4%)
cocaine use	0% (0-2%)	0% (0-10%)
sexual activity	36% (27-45%)	29% (17-42%)

The students reported more cigarette and alcohol use by Randomized Response, low levels of marijuana and cocaine use by both methods, and similar levels of sexual activity by each method. We conclude that (a) Randomized Response can be a useful method to determine substance use levels among students who might otherwise not provide accurate information, and (b) use of marijuana and cocaine may indeed be lower for students enrolled in school-based clinics than those who do not attend the clinic or may not attend school at all.

What Happens After Preschool Vision Screening in **Pediatric Practice?**

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Half of all children with amblyopia are diagnosed after age 5, when therapy is no longer effective. Although many late-diagnosed amblyopic children have never had vision screening (VS), recent data suggest that as many as one-third have had previous screening. We analyzed data from the PROS VS study to identify what happens after preschoolers have VS in pediatric practice.

Pediatricians in 102 PROS Network practices collected data on children ages 3-5 years seen for check-ups from May to July of 1988. Parents were asked to fill out a questionnaire. Parents of children who failed either VS or the cover-uncover test were

mailed a follow-up (F/U) questionnaire 2 months later.

Pediatricians enrolled 8417 children. The 7754 (92%) whose parents completed the questionnaire comprise the study sample. Over 95% of mothers had a high school education and 87% of the sample were White. Twelve percent had already seen an eye specialist for evaluation and 63% had never had VS. Sixty-six percent of the sample (including 64% of those never before screened) had VS at the visit. Using AAP guidelines, 9% of those screened failed acuity VS and 5% failed binocularity VS. An additional 1% failed only the cover-uncover test on physical exam. Disposition for those who failed a VS test was as follows: 21% were newly referred to a specialist, 57% were told to return to the office for repeat screening in 1-36 months, 5% were referred back to their eye specialist, and 15% were told to recheck as needed. Families whose child had failed either VS or the cover-uncover test were mailed a F/U questionnaire and 49% responded. Fiftyone percent of these families were unaware that their child had failed a test. Another 9% were aware of the results and had plans to make a future F/U appointment. Only 33% had either already made or kept a F/U appointment.

Previous studies have shown that over half of U.S. preschoolers don't receive VS. Our results suggest that even when VS is performed, the process may be characterized by miscommunication and poor F/U. These results may explain how VS, even if properly performed with a low false negative rate, could fail to prevent amblyopia in preschoolers seen in pediatric practice.

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The Pediatric Forum

This department of AJDC is reserved for comment, criticism, observation, and discussion of "issues of current concern and importance for children's health." The Editor encourages our readers to express themselves on a variety of topics and issues. Further, we encourage the submission of unique and brief clinical and scientific observations that do not fulfill the criteria for original articles.

Management of Coin Ingestion

Sir.—I read with interest the articles by Schunk et al1 and Caravati et al2 and Dr Fulginiti's editorial3 in the May 1989 issue of AJDC on the management of coin ingestion. Dr Fulginiti, the reviewers, and the editorial staff were startled to find that over 70% of the pediatricians surveyed in Salt Lake City, Utah, would not have obtained a roentgenogram of an asymptomatic child who had ingested a coin. I have been a practicing pediatrician for 23 years and I, too, would not have sent the asymptomatic child to the emergency department. I would like to comment on the Schunk et al article and on the literature on coin ingestion, and present a few of my own findings and observations.

1. The editors have not served the readers of this journal well in publishing the part of the summary in the Schunk et al article that states that "All children who swallow coins should undergo roentgenographic evaluation." That portion of the summary can in no way be derived from the material presented in the article. The authors described nine children without symptoms who demonstrated an esophageal coin on roentgenogram. In four, the coin was removed, and in an additional two, the parents decided not to wait 24 hours to see if the coin would pass through the intestine into the diaper. The remaining three asymptomatic children passed the coin in the next 201/2 hours. The only conclusion I can draw from the Schunk et al article concerning coins lodged in the esophagus of asymptomatic children is that, in all three cases, the coin passed. Why then obtain roentgenograms on all?

2. Articles on coin ingestions in the literature are reports of experiences in emergency departments with up to a few hundred reports of coin ingestions or reports of complications resulting from the erosion of coins

through the esophagus. None of the published articles answers the quéstion: What is the natural history of coins lodged in the esophagus of asymptomatic children? Without knowing the natural history, one cannot estimate the magnitude of risk in not obtaining a roentgenogram of the asymptomatic child with recent coin ingestion. It is for this reason, I suspect, that the authors of the articles on coin ingestion in the major textbooks of pediatrics have skirted the issue of what to do with the asymptomatic child with recent coin ingestion. I would suggest that the 70% of pediatricians who would not refer asymptomatic children with coin ingestions for roentgenograms are pediatricians whose experience tells them that the risks and costs of the emergency department visit exceed the risk of complications that might arise from an esophageal erosion.

3. I recently surveyed 200 consecutive children in my practice over the age of 5 years to estimate what percentage of my patients ingested coins. I found that 20 (10%) of 200 children had at one time ingested a coin. I practice in Nassau County, Long Island, New York, where there have been 280000 births in the last 20 years. I estimate that in the past 20 years there have been 10%×280000 or 28000 coin ingestions in Nassau County. This is probably a low estimate since many children ingest coins on multiple occasions and because many coin ingestions are never discovered. In an attempt to discover late complications from earlier coin ingestions in Nassau County in the past 20 years, I surveyed the practices of all 10 pediatric surgeons in the county, all 4 pediatric radiologists in the four teaching hospitals serving the county, the chiefs of pediatrics of all 13 hospital pediatric departments in the county, and the practices of 20 ear. nose, and throat surgeons in the

county. I found 7 children who, at some point (days, weeks, or months) after a coin ingestion, presented to a medical facility because of stridor (4 cases) (Jack Levenbrown, MD, oral communication, 1989) (John Leonidas, MD, oral communication, 1989), dysphagia (2 cases, one of which involved an esophageal abscess) (Mark Goldstein, MD, oral communication, 1989) (Merrill Goodman, MD, oral communication, 1989), and recurrent pneumonia (1 case) (Stuart Selkin, MD, oral communication, 1989). The seven coins were removed from the esophagus uneventfully during esophagoscopy or by Foley catheter. There was 1 additional child (Elizabeth Coryllos, MD, oral communication, 1989) who underwent a thoracotomy for removal of a penny that had eroded through the esophagus. This 16-month-old child had reportedly been fed a penny by his 3vear-old sibling at age 3 months. A chest roentgenogram was obtained at 16 months because of a persistent cough following an episode of bronchitis. The penny was lodged in the space between the esophagus and the trachea at the level of the tracheal bifurcation. During the operation, the coin slipped back into the esophagus and up into the posterior pharynx from where it was manually extracted. The postoperative course was benign. It is not clear whether the persistent cough in the 16-month-old child was related to the presence of the coin or if the coin might have remained in place indefinitely without causing symptoms.

In summary, I would estimate that in the past 20 years in Nassau County, over 28 000 coin ingestions resulted in one major complication that led to major surgery. If it is true on Long Island, as suggested by the Schunk et al¹ data in Salt Lake City, that over 70% of the asymptomatic coin ingestions are not followed up roentgenographically, then the scarcity of major

complications cannot be attributed to the aggressive search for coins in children with recent coin ingestions.

I can now present to the parents of my patients with coin ingestions the magnitude of the risk of not obtaining a roentgenogram of the asymptomatic child. My own conclusion is that the inconvenience, cost, radiation exposure, psychological trauma, and other possible problems from the emergency department visit, and from esophagoscopy, anesthesia, and catheter removal of coins, exceed the risk of watchful waiting.

I would propose the following management of coin ingestions in children for the private practitioner:

- 1. Over the age of 2 years, no emergency department visit or roentgenogram of the asymptomatic child with a recent coin ingestion unless the child is retarded or has an esophageal problem.
- 2. Under the age of 2 years, screen diapers of the asymptomatic child for 1 week—if no coin is discovered, then discuss with parents the pros and cons of obtaining a roentgenogram.
- 3. For all children with a recent coin ingestion, symptomatic or asymptomatic, encourage food and fluids and delay obtaining a roentgenogram as long as possible.

Further studies to determine the need of obtaining roentgenograms of the asymptomatic child with a recent coin ingestion should be based on retrospective surveys similar to the one presented here. Prospective studies from emergency departments that would include a policy of nonintervention with extended watchful waiting are generally unacceptable to parents and hospitals because of logistical, emotional, and legal considerations, and the numbers are too small for major complications to be expected.

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In Reply.—We would like to thank Dr Joseph for his comments and interest in our recently published article concerning coin ingestions.¹ It was our impression, and Dr Joseph's letter supports this, that the practice of not obtaining a roentgenogram of the asymptomatic child following a coin ingestion is common nationwide. Part of the impetus to do this study was this discrepancy between published recommendations and actual practice. Dr Fulginiti further examined the determinants of standard care and standard practice in the accompanying editorial. We would like to address a few of the points mentioned by Dr Joseph.

1. Though it is tempting to conclude that all asymptomatic patients with an esophageal coin who had a chance to be observed for spontaneous passage into the stomach actually did pass the coin, the number of patients that did so was only three. It is impractical to make a practice recommendation based on three cases. Furthermore, during the study there were two impactions demonstrating that spontaneous passage cannot be guaranteed even if the patient is given time. In addition, since our study was accepted for publication, we have seen a 2-yearold child with an esophageal coin that had eroded through the mucosa. This child required a thoracotomy and an esophagotomy to remove the coin with a cost and morbidity that was not insignificant.

2. The question regarding the actual natural history of swallowed coins is a good one and we hope that future studies will more adequately address this issue. In presenting the study, it was not our intention to imply that a visit to the emergency department was absolutely necessary in the asymptomatic child, but rather that a roentgenogram be obtained. The optimum timing of the roentgenography in the asymptomatic child has not been defined but, as we speculated in our article, it is probably not an emergent problem.

3. We applaud Dr Joseph's efforts to determine the exact risk of serious complications from a coin ingestion through personal recollection and estimation of frequency of coin ingestions during the last 20 years in Nassau County. There are, of course, significant inherent methodologic problems with this retrospective type of survey.

The data from our study cannot support his proposed management scheme. We would strongly disagree with the suggestion that even in the symptomatic child, liquids and solids be attempted and roentgenography delayed. It is inconsistent that Dr Joseph notes that a policy of "extended watchful waiting" would be unacceptable to parents and hospitals because of logistical, emotional, and legal considerations, yet feels that any actual risk to the patient is remote.

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Pediatric Coin Ingestion

Sir.—I read with interest, in the May 1989 issue of AJDC, the conflicting conclusions by different authors from the same university regarding the question of routine chest roentgenography in the evaluation of esophageal foreign bodies in children. 1.2 Schunk et al1 recommended that all such children be evaluated, as previously suggested by Hodge et al.3 Caravati et al.2 however, concluded that evaluating asymptomatic children is unnecessary provided the enteral administration of liquids is tolerated and telephone follow-up is available. The latter conclusion is incredible considering the report of esophageal perforation by a coin in a 31/2-year-old child who had been asymptomatic for 6 months following the ingestion.4 The definitive thoracotomy would have been avoided if the parents had sought medical attention initially, a chest roentgenogram had been performed, and the coin had subsequently been removed.

An 11-month-old male infant with a similar history was referred to our emergency department (ED) because of a right parieto-occipital skull fracture. The anteroposterior view of his skull series obtained at the outlying hospital revealed an apparent coin in the cervical esophagus. An anteroposterior roentgenogram of the neck, chest, and abdomen at our hospital confirmed the location of the foreign body in a coronal position. He had no

history of foreign-body ingestion to the parents' knowledge, and they denied any gastrointestinal or respiratory symptoms. There were no sequelae from the head trauma following admission, but esophagoscopy allowed removal of a penny and revealed erythema and edema of the esophageal mucosa. The occurrence of a skull fracture was fortuitous, since our patient might have otherwise experienced an outcome similar to the patient described by Nahman and Mueller.

One can only conclude from these cases that a thoracotomy is not an acceptable method for removing coins from the esophagus in young children, regardless of whether they are symptomatic at the time of ingestion. Children with coins impacted in the esophagus, especially at the cricopharyngeus, must be identified promptly, and telephone follow-up is not acceptable in the management of infants and toddlers. Caravati et al2 do not mention the ages of eight symptomatic patients who spontaneously passed the coin into the stomach. The mean patient age in their study, however, was 3.5 years, the same age as the child who was asymptomatic for 6 months.4 They admit that complications after the last telephone call on day 5 would be missed by their method as it is presented.2

There will remain a debate over the ideal method for the removal of smooth, esophageal foreign bodies. Endoscopy using general anesthesia carries the attendant risks and expenses of both procedures, 5-9 albeit the actual incidence of complications is low. Endoscopy is the method of choice if the patient has swallowed a sharp object, 5,9 presents with respiratory distress, has a history of preexisting esophageal abnormalities,9 or the foreign body has been present for more than 24 to 48 hours. 5,6 O'Neill et al,9 however, have used the Foley urethral catheter technique with fluoroscopic guidance in a few patients whose esophageal foreign bodies appeared to have been present for several days or weeks.

This procedure has been utilized on an outpatient basis and recommended by different authors for over two decades to remove blunt^{5,6} and smooth^{7,9} foreign bodies from the esophagus. It has even been used to remove toy jacks,^{5,7} as well as different-sized coins.^{6,9} Coins have been successfully removed in most cases but sometimes

are pushed into the stomach and pass uneventfully through the gastrointestinal tract.^{3,9} Like other authors,^{3,5-8} O'Neill et al⁹ experienced no complications when treating 62 patients in this manner during a 10-year period. The Foley technique remains the method preferred by Schunk et al.¹

This is a simple maneuver during which a 10F, 12F, or 16F Foley balloon catheter is passed through the nose^{5,6,8,9} or mouth into the esophagus past the foreign body. The patient may be placed in the Trendelenburg position,6 and the head is held to one side. 5-9 The balloon is inflated with air or normal saline solution,6-8 and the catheter is withdrawn gently^{6,7,9} but must sometimes be done quickly to overcome the upper esophageal peristalsis. Suction equipment must be readily available, and it has been suggested that a tracheostomy tray be set up should the patient experience laryngospasm.6 The physician should also be prepared to resuscitate the child with a bag and mask, a source of oxygen, a laryngoscope with the appropriate size blade and endotracheal tube(s), and intravenous medications as dictated by a cardiac monitor. Aspiration of any size coin into the trachea is unlikely in the infant or toddler, because the external diameter of a 4.0-mm or 4.5-mm (internal diameter) endotracheal tube used at these ages, and thereby the diameter of the vocal cords, is smaller than the diameter of a dime. McGill forceps should be available for the rare instance one might have to remove the coin from the hypopharynx under direct laryngoscopy. Normally the child spits out the coin when it reaches the oropharynx6 or it can be retrieved at this time by the examiner's fingers. 5,8 Guidance using fluoroscopy is, therefore, not essential to successfully removing the coin6 but does involve additional expenses and radiation. It is for all these reasons that I prefer to do the procedure in the ED where all of the necessary equipment and supplies are available and the personnel are much more experienced in pediatric resuscitation, which can be skillfully performed if the occasion should ever arise.

I have removed several pennies and a bolt with a wide head from the cervical esophagus with this technique in the ED. The only complication occurred when a patient bit my index finger during removal of the penny from his oral cavity! A small amount

cf bleeding may be noted from passage cf the Foley catheter, and one must remember to deflate the balloon before withdrawal through the nose. The patient should be conscious and does not reed sedation since the entire procecure takes less than 1 minute when properly performed. The procedure is safe in the hands of a physician who is skilled in pediatric resuscitation, but informed consent should be obtained. The parents should be given the option cf endoscopic removal with the patient under general anesthesia and informed of the relative risks of both methods. No parent has yet to opt for endoscopy when I have offered them the choice of procedures.

In summary, the need for roentgemography is dictated by the chief complaint of coin ingestion, not by the
presence or absence of symptoms. The
Foley catheter technique is a safe alternative to the risks and expenses
incurred with endoscopy and general
anesthesia. It may be done without
fluoroscopy in the ED by a physician
skilled in pediatric resuscitation.

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In Reply.—We appreciate Dr Foster's interest in our article. Although the authors of the two studies^{1,2} in question may have faculty appointments at the same university, the studies were

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performed independently, without knowledge of one another, and on entirely different patient populations. Dr Schunk and associates² evaluated 52 patients presenting to an ED of a tertiary care children's hospital during a 12.5-month period. Some of their patients were referred to their institution specifically for coin removal. We prospectively studied 162 patients during a 28-month period who voluntarily called the Intermountain Regional Poison Control Center with a complaint of coin ingestion. There is evidence that children presenting to EDs are at a twofold to sixfold greater risk for symptoms, complications, and hospitalization from foreign-body ingestion than those presenting to an office practice with the same complaint.3 This suggests that the ED population represents a higher-risk group and may not reflect the outpatient population as a whole. The "conflicting" results between our studies illustrate this difference in patient populations, and we do not recommend generalizing conclusions from one group of patients to the other.

There have been serious complications reported from prolonged esophageal impaction of coins. What is the frequency of this occurrence? Of the 10 785 cases of coin ingestion voluntarily reported to the American Association of Poison Control Centers (AAPCC) national database during 1985 through 1988, only 3 (0.03%) resulted in "major medical outcomes." There were no deaths.4-7 Thus, major complications seem to be extremely rare. In this era of cost containment, it seems reasonable to look for reliable criteria to selectively screen this patient population for roentgenography referral without significantly increasing their risk of a poor outcome. This could result in thousands of children avoiding ionizing radiation exposure and ED costs each year.

Anecdotal case reports serve a useful purpose in the medical literature by suggesting hypotheses about observed clinical events. However, we believe that guidelines for clinical practice should be based on more reliable scientific data whenever possible. Dr Foster's case of the "fortuitous" skull fracture has little bearing on our study or conclusions because there was no history of coin ingestion in his patient. Our study conclusions are based on carefully collected and analyzed prospective patient data. The mean age of the eight sympto-

matic patients who spontaneously passed the coin was 3.5 years, the same as the population as a whole. We also found that patients younger than 3 years were no more likely to have lodged esophageal coins than those older than 3 years. In our patient population, we believe that it is reasonable to allow observation at home for the child who is asymptomatic and tolerates oral fluids well at the time of ingestion. Physicians may increase their comfort level in managing the asymptomatic patient at home by excluding those who ingest quarters (which were statistically more likely to result in impaction and symptoms than other coins) and by referring for roentgenography infants and toddlers who do not pass the coin into the diaper within 1 or 2 days. All patients who have any symptoms after the ingestion should be immediately referred for roentgenographic location of the coin, even if the symptoms are transient.

Our study is not definitive. Studies of much larger patient populations with long-term follow-up are needed to confirm our initial observations and to detect any possible adverse outcomes that may be associated with these recommendations. However, the fact that the majority of physicians in Utah1,2 and nationally4-7 manage the patient with the complaint of "coin ingestion" outside health care facilities raises questions on what really is the standard of practice.8 Consequently, what should be the null hypothesis of these future studies? Should we try to disprove that roentgenography is mandatory (the assumption being that mandatory roentgenography is the standard) or disprove that selected patients can be managed outside health care facilities (the assumption that mandatory roentgenography is not the standard)?

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β-Hemolytic Non-Group A Streptococci and Pharyngitis

Sir.—The approach taken by Hayden et al¹ in using a case-control study to assess the association of β -hemolytic non-group A streptococci and pharyngitis should be commended, since this design was not currently employed by authors of most reports that we previously reviewed.² However, although the anaerobic incubation may maximize isolation of β -hemolytic non-group A streptococci, the increased isolation rate may not necessarily apply to those that are likely to be pathogenic.²

There is little evidence to implicate either β-hemolytic group B or group F streptococci as causative agents in pharyngitis.3,4 As suggested by Hayden et al, and our previous review,2 groups C and G have been incriminated in several outbreaks. Subsequent to these outbreak reports, however, basic science investigations in the genetics of group C and group G microorganisms have revealed that each of these Lancefield groups possesses more than one distinct species.2 Perhaps most important in this distinction is the separation of large-colony B-hemolytic group C and group G streptococci from the small-colony \beta-hemo- ${\bf lytic}\ Streptococcus\ anginosus\text{-}milleri$ group, which may possess group C and group G Lancefield antigens. It is speculated that the latter bacteria are probably not pharyngeal pathogens. The latter bacteria are genetically related to most group F streptococci and in our experience consistently constitute approximately 40% to 70% of β-hemolytic Lancefield group C and group G streptococci from pediatric and adult populations. Although outbreak reports have not benefited from the above findings, Streptococcus zooepidemicus among the large-colony β-hemolytic group C streptococci is more clearly associated with pharyngitis. 5,6 Since carbon dioxide in the growth atmosphere enhances the hemolysis of β -hemolytic S anginosusmilleri group, 7 it is possible that the increased isolation rate of β -hemolytic non-group A streptococci in an anaerobic environment mainly reflects the increased isolation of these putatively nonpathogenic bacteria.

Thus, while the study of Hayden et al may confirm the lack of importance of group F streptococci and, to a lesser degree, group B streptococci in pharyngitis, further case-control studies are required to test the association of group C and group G streptococci with sore throats.

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In Reply.—We agree with Dr Cimolai in three important respects: First, many of the non-group A streptococci that are detected only through the anaerobic culture technique may not be pathogenic. Careful speciation of non-group A organisms isolated using anaerobic vs conventional culture techniques would be a valuable first step in determining whether the increased anaerobic isolation of non-group A organisms is clinically relevant.

Second, the category "non-group A streptococci" is not homogeneous. Certain non-group A streptococci, especially those from the Lancefield group C, appear much more likely

than others to cause pharyngitis. Even within the serogroup C, certain species have been recognized primarily as veterinary pathogens whereas other species have been associated more often with human illness. Further investigations should most logically focus on those species most closely associated with clinical pharyngitis.

Finally, the basic issue of how often non-group A streptococci cause pharyngitis remains unsettled. Our data suggest that non-group A organisms were not a major cause of pharyngitis in the population we studied, and document the importance of including carefully age-matched controls in the study design. We are pursuing further epidemiologic studies of group C streptococci among young adults with symptomatic pharyngitis. Additional controlled studies with serologic correlation will, we hope, clarify this interesting clinical problem.

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Poliovirus Vaccine Policy

Sir.-I have several comments on the discussion of polio immunization policy for children presented by Marcuse1 and Katz² in the September 1989 issue of AJDC. In the past, the real risk of oral polio virus vaccine (OPV)-related polio has probably been closer to 1 case per 100000 persons immunized. The state of Washington had about 1 case annually for many years. The rate may be lower nationally, but that is most likely a problem of lack of recognition and/or reporting. Additionally, OPV can cause nonparalytic illness, which usually goes unrecognized unless the vaccine virus is picked up inadvertently when spinal fluid is cultured and the patient is then asked about possible OPV exposures (Bruce G. Weniger, MD, MPH; David Remis, MD; Mark Heerema, MD; et al, unpublished case, October 1982). Perhaps the type III component in vaccine is now less apt to revert to neurotoxicity, but can this be certain?

Thirty years ago the ethical argument against the secondary spread of OPV virus was less compelling than today because wild virus was quite prevalent and presented a greater risk of causing illness than the vaccine virus. Now it is questionable whether it is ethical to subject those who do not

receive the vaccine to this risk. Yet, more nonrecipients than recipients of OPV have developed OPV-related polio.

In addition, the cost of polio vaccines relates mostly to litigation, not to cost of production. Twenty years ago polio vaccines cost about 10 cents per dose. If vaccine-related injury decreases, so will the cost of vaccines.

Giving two injections instead of one and using two polio vaccines should present few problems. This procedure was common in the past and re-creates the situation we faced with polio vaccines in the late 1950s and early 1960s. We also faced it with the measlesmumps-rubella vaccine components. It is a minor inconvenience. Additionally, the use of one immunization approach privately and another by health departments may not be desirable, but it has been the case for most of the past three decades, especially when new vaccines were introduced. Indeed, with the mumps vaccine, the introduction by health departments was so late in most of the country that the epidemiology of the natural spread of the disease was so interfered with that low-income children ended up with a much greater risk of developing natural mumps later in life. However, in the case of polio, that is not the kind of choice that would present.

I have long believed that infants should be initially immunized with diphtheria and tetanus toxoids and pertussis vaccine-P (Quadrigen) whether or not the inactivated polio virus vaccine was enhanced, and then OPV might be used for toddlers and at school entry. A single dose of OPV results in 85% to 90% seroconversion to all polio virus types, and the result from a herd immunity perspective would not change from such a schedule use. Most adults have been exposed to OPV or wild virus; therefore, spread of OPV virus from recipients to others serves little purpose. The problem of susceptible population subgroups will remain regardless of vaccine policies. To reach them requires special facilitating mechanisms directed to the groups.

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In Reply.—Dr Bader's thoughtful comments merit consideration now and for the future. If, indeed, the state of

Washington has a vaccine-associated paralytic polio rate of 1 per 100 000, it differs markedly from the rest of the nation where careful surveillance and annual review of reported alleged cases by an expert committee have consistently disclosed an overall rate of 1 per 2.7 million poliovirus vaccine live oral trivalent (TOPV) doses or 1 per 560 000 first doses of TOPV. From 1975 to 1986, 107 cases were labeled vaccine-associated paralytic disease, of which 37 were in recipients and 48 in contacts. If Washington has a higher rate, it may resemble the unexplained geographic (or possibly genetic) aberrations observed in some other infectious diseases studies such as the unusual results in Minnesota with the initial studies of Haemophilus influenzae type B polyribose phosphate vaccines in contrast to the efficacy studies in most other states.

Dr Bader writes on the one hand that "it is questionable whether it is ethical to subject those who do not receive the vaccine to this risk" but later states that "most adults have been exposed to OPV or wild virus; therefore, spread of OPV virus from recipients to others serves little purpose." The proposed benefits of vaccine virus spread were intended for unimmunized, susceptible infants and children rather than adults.

The proposed program of enhanced potency inactivated polio vaccine (E-IPV) at ages 2 months and 4 months followed thereafter by TOPV is one that I fully support. A similar schedule in Denmark has been successful for many years. However, in our country we need to answer several questions before such a new program should be initiated.

1. Is acellular pertussis vaccine as effective as the whole cell product?

2. If the answer to question No. 1 is affirmative, can we concoct a DTP-E-IPV in which the P component is acellular without diminishing the efficacy either of E-IPV or of P?¹

3. Once No. 2 above has been achieved, can we provide such a new multivalent vaccine (perhaps also to include conjugate *H influenzae* type B) followed by TOPV to all infants while maintaining freedom in the United States from circulation of imported strains (Mexico, Brazil, Peru, Colombia, Venezuela) of virulent polioviruses?

4. Can we afford—or will our legislatures appropriate—the necessary funds to implement such a program for all of our nation's infants? (Vaccine

program costs would be far less than the price of a single B-2 bomber.)

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Erythema Infectiosum ('Fifth Disease') Exposure During Pregnancy

Sin-Human parvovirus (B19) is now known to be the causative agent of erythema infectiosum (EI) or "fifth disease." Ervthema infectiosum is characterized by a distinctive facial rash, giving a "slapped cheek" appearance. Although fever, a generalized lacy rash, minor gastrointestinal or respiratory symptoms, or arthralgias may be noted, most children have mild disease.1 Erythema infectiosum occurs in epidemics, most often in late winter or spring, and outbreaks of EI in elementary or junior high schools are frequent. Inevitably, pregnant mothers or teachers of infected children will be exposed to parvovirus.

Patient Report.—A 35-year-old healthy woman, gravida 3, para 3, became pregnant in March 1989 and had an uneventful first trimester. At 10 weeks of gestation, an outbreak of EI that centered in the elementary schools occurred in her community. All three of the patient's children developed a mild febrile illness with the characteristic facial rash. At 11 weeks of gestation, the patient noted a faint macular crythematous facial rash with a few similar abdominal lesions accompanied by mild posterior cervical lymphadenopathy. These symptoms resolved spontaneously without treatment.

At 13½ weeks, the patient suffered a spontaneous abortion. The fetus and placenta were normal on gross inspection. Pathologic examination did not reveal any chromosomal, developmental, or infectious abnormalities. Parvoviral studies were not performed.

Two weeks following the abortion (5 weeks following the maternal rash illness), serologic evaluation of the patient revealed positive IgG and IgM parvovirus B19 titers. Fetal tissue was not available for testing.

Comment.—Only 30% to 60% of adults have detectable IgG antibody against parvovirus B19.2 Erythema infectiosum is such a common disease that it is inevitable that some suscep-

tible pregnant women will be exposed through contact with schoolchildren. Viremia, the most intense period of contagion, occurs during the week prior to the appearance of the diagnostic rash so it is almost impossible to prevent secondary cases in households or school exposure. Exposure to sporadic cases of EI is also unavoidable. Even during epidemics, it may be impractical for a pregnant schoolteacher to avoid contacts, as an outbreak may last weeks to months.

A serious outcome of EI outbreaks is fetal loss associated with acute maternal parvovirus infection.2-5 Stillbirth, nonimmune fetal hydrops, and spontaneous abortion have all been reported with proved maternal infection. The exact risk of fetal death following parvovirus infection in a nonimmune pregnant woman is unknown but is estimated to be approximately 5%. Infants who survive fetal infection have no adverse sequelae and do not shed the virus after birth. Neither the severity of the maternal infection nor the timing during gestation are correlated with pregnancy outcome.

Immunologic tests to document infection with or immunity to parvovirus are not readily available; only one commercial laboratory, university research laboratories, and some state health laboratories (in cooperation with the Centers for Disease Control, Atlanta, Ga) provide such testing. Routine immunologic screening for parvovirus of all pregnant women, or even of pregnant women in contact with children, is not recommended, as no vaccine or other prophylactic measure is available to protect susceptible women.

In the case of known exposure of a pregnant woman, the risk to the fetus may be estimated by maternal serologic studies. The presence of anti-B19 IgG antibody alone documents past immunity; there is no risk to the fetus. The presence of anti-B19 IgM antibody, with or without IgG, documents recent infection. Guidelines for following up such pregnancies have been published.2,5-7 Although the risk of fetal death is low, probably less than 5%, the mother should receive anticipatory guidance concerning this possibility. Some authorities recommend followup with periodic ultrasound examination or alpha-fetoprotein determination for early detection of fetal hydrops.

The pediatrician has two roles in the prevention and/or evaluation of parvovirus infection during pregnancy.

First, when making the diagnosis of EI in a child, the family should be counseled. A pregnant woman in the household should be referred immediately for appropriate obstetric care. In our patient, the pediatrician did not inquire about the mother's pregnancy status. The obstetrician was notified of the maternal illness but did not recommend any follow-up. Thus, any opportunity to prepare this family for the possibility of fetal death was lost.

Second, the pediatrician has a role in defining local school or public health policy. The Centers for Disease Control and the American Academy of Pediatrics have recently published guidelines for counseling pregnant workers exposed in schools or daycare centers.2,8 Such information should be made available by pediatricians and school health officials during epidemics. In our patient, the school sent a letter notifying parents of the outbreak and describing typical disease; no mention was made of risks to exposed pregnant women. The public health department did not have available any guidelines on exposure risks or follow-up care.

Although the outcome in this instance could not have been prevented, it was important to the family to have a definite explanation of the fetal loss and to reassure them that it would not recur in subsequent pregnancies. Pediatricians have a responsibility to explain this hazard to their pregnant patients.

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Management of Diabetes in Pediatric Resident Clinics

Sin-In the October 1989 issue of AJDC, Kronz et al' described a method that would, it is hoped, improve the care given by pediatric residents to their continuity patients with insulin-dependent diabetes mellitus. Although pediatricians treat patients with insulin-dependent diabetes mellitus in their practices, the scope of their role in the management of this chronic illness is debatable.

As noted by the authors, caring for the child with insulin-dependent diabetes mellitus requires the time and commitment of many skilled professionals: physicians, educators, dietitians, psychologists, and social workers. The general pediatrician rarely has access to these personnel in his or her office and therefore the patients and their families may not see all members of the team in a coordinated fashion. Furthermore, the pediatrician rarely has the expertise in these areas to serve as these other professionals would. Additionally, few pediatricians have the time to keep up with recent advances in diabetes research that affect the care of their patients.

Thus, as outlined by Schreiner and Travis.2 we believe that the patient's pediatrician, although an integral part of the diabetes team, should not necessarily be the person solely responsible for overseeing or coordinating the management of the child's diabetes. Only if the pediatrician has a special interest in the child with diabetes, keeps up with the recent advances in the field, and can easily access the other team members should this person lead the diabetes management team. Thus, although residents should be familiar with the principles of good and adequate care of children with diabetes, they should not automatically be the physician primarily responsible for the provision of this care. The authors' results document that even with the best reminders, such a system does not work; it is unlikely that care would improve after the resident enters practice.

Thus, rather than concluding that their data "indicate a need for improved instruction of pediatric residents," we would conclude that residents should not be primarily responsible for the care of children with diabetes mellitus, but rather an attempt should be made to integrate them into the diabetes team headed by a diabetologist. This would more

closely resemble the role, we believe, that the general pediatrician should assume in practice.

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In Reply.—We appreciate the interest of Drs Brouhard and Cunningham in the question of who should care for children with diabetes. Obviously, there are many opinions but no right answers to the question of whether a general pediatrician or a subspecialist should be primarily responsible for the care of children with chronic illnesses such as diabetes. We agree about the need for active involvement of a multidisciplinary team in pediatric diabetes care. It is not clear, however, that such a team necessarily needs to be in a traditional tertiary care setting.

We can envision alternative models in which a tertiary care program works to support a team of nurse educators, dietitians, and mental health professionals in a community hospital who, in turn, provide support to community pediatricians. In that we have clearly documented the active and often sole involvement of general pediatricians in diabetes care,1 and in view of the increasing shortage of pediatric endocrinologists in many geographic areas, it is important to continue to evaluate new approaches to training general pediatricians in caring for patients with diabetes.

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*From the American Academy of Pediatrics Committee on Nutrition statement. Fluoride supplementation: Revised dosage schedule. *Phdiatrics 1986;77(5):785-761.

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Leads From the MMWR

Morbidity and Mortality Report
Centers for Disease Control, Atlanta

Measles—United States, First 26 Weeks, 1989

During the first 26 weeks of 1989, local and state health departments reported a provisional total of 7335 measles cases to CDC-a 380% increase over the 1529 cases reported for the same period in 1988; at least 10 measles-associated deaths were also reported. In addition, another 30 suspected measles-associated fatalities are being investigated by local and state health departments and CDC. Forty states and the District of Columbia reported cases, compared with 36 states for the first 26 weeks of 1988. During the 1989 period, the incidence rate was 3.0 cases per 100 000 population—five times the rate of 0.6 per 100 000 for the same period in 1988 and more than double the rate for all of 1988 (1.4 per 100 000).1

Thirteen states reported at least 100 cases and accounted for 6588 (89.8%) of all reported cases: Texas (2764), California (1189), Ohio (661), Illinois (489), New Jersey (271), Missouri (237), New York (193), North Carolina (167), Pennsylvania (147), Connecticut (146), Nebraska (110), Kansas (108), and Oklahoma (106). Incidence rates of >4.0 per 100 occurred in Texas (16.4), Delaware (8.9), Nebraska (6.9), Ohio (6.1), Missouri (4.6), Connecticut (4.5), Kansas (4.3), Illinois (4.2), California (4.2), and Rhode Island (4.1).

For 6880 (94%) cases, more detailed information was collected by CDC. Of these, 6373 (92.6%) met the clinical case definition for measles,* and 1775 (25.8%) were serologically confirmed.

Consistent with the usual seasonal pattern, most of the 6880 cases occurred from March through May (weeks 9-19). Ninety-three (1.4%) cases were imported from other countries; an additional 157 (2.3%) cases were epidemiologically linked to imported cases.

One hundred twenty-eight outbreaks involving five or more persons were reported and accounted for 78.8% of the 6880 cases. Almost half the cases occurred in outbreaks involving 100 persons. The three largest outbreaks occurred in Houston, Los Angeles, and Chicago and accounted for 31.9% of the 6880 cases. Twenty percent of all cases were reported from the outbreak in Houston.

Detailed information on age was provided for 6873 (99.9%) cases. Children <5 years of age accounted for 30.2% of measles cases, compared with 19.4% during the same period in 1988. Of this group, 664 (32.0%) were <1 year of age. School-aged children (5-19-year-olds) accounted for 51.1% of cases in 1989 but for 66.2% of cases in 1988. The incidence rates for all age groups were higher in 1989 than in 1988; the highest were for 0-4-year-olds (11.3 per 100 000).

Complications were reported in 672 (9.8%) cases, including otitis media in 318 (4.6%) cases, pneumonia in 178 (2.6%), diarrhea in 171 (2.5%), and encephalitis in five (0.1%). Nine hundred thirteen patients (13.3%) were hospitalized, and 10 measles-associated fatalities were reported (casefatality rate: 1.5 deaths per 1000 reported cases). Eight of the deaths were reported in children <5 years of age, all of whom were unvaccinated. None had a reported underlying illness or immunodeficiency. Most deaths have been attributed to pneumonia.

The setting of transmission was reported for 4057 (59.0%) cases: 1899 (46.8%) persons acquired measles in primary or secondary schools; 796 (19.6%) in colleges or universities; 627 (15.5%) at home; 248 (6.1%) in medical settings; 89 (2.2%) in day-care centers; and 398 (9.8%) in other settings, including work, church, and the military. The number of cases occurring in colleges and universities was 60.7% higher than those from the same period in 1988.

A total of 3520 (51.2%) measles patients had been vaccinated on or after

their first birthday, including 1298 (18.9%) who had been vaccinated between the ages of 12 and 14 months; 3340 (48.5%) were unvaccinated or vaccinated before their first birthday. Of the 6873 patients for whom age information was provided, 3512 (51.1%) were school-aged children, 2830 (80.6%) of whom had been appropriately vaccinated. As in 1988, most vaccine failures occurred in 12-19year-olds, and children <2 years old were most affected. Measles occurred in 1261 (18.3%) persons for whom vaccine was not routinely indicated. and 226 (3.3%) were unvaccinated for other reasons. Of those unvaccinated, vaccine would have been routinely indicated for 1853 (55.5% [26.9% of total]). The percentage of cases in unvaccinated persons for whom vaccination was indicated varied by age group. Most occurred among children 16 months to 4 years of age (64.7%) and among persons 20 years of age (52.9%).

Reported by: Div of Immunization, Center for Prevention Svcs, CDC (MMWR Vol. 38, No. 51).

Editorial Note: In 1989, measles outbreaks have involved previously vaccinated school-aged children and college students, as well as unvaccinated urban preschoolers who are predominantly black and Hispanic.2 Large outbreaks involving minority populations are continuing in Houston, Los Angeles, and Chicago. Aggressive outbreak-control strategies aimed toward reaching inner-city children have been implemented and include intensified surveillance, door-to-door vaccination in high-risk communities, emergency department vaccination clinics, and lowering of the recommended age for vaccination to 6 months during outbreaks, with revaccination at 15 months.

The increased incidence of measles in preschoolers living in densely populated urban areas reflects low vaccination levels in these populations. While these children are generally well immunized by the time they enter school, immunization levels in some inner cities are as low as 49% in children 2 years of age.3 Many of these children receive intermittent health care and are less likely to be ageappropriately immunized with other antigens.4 Innovative efforts need to be directed toward reducing barriers to immunization services and toward full use of existing opportunities to vaccinate eligible children whenever they present for health care. This approach should increase opportunities for vaccine administration in highly susceptible populations and reduce transmission to infants too young for routine immunization.

Suboptimal vaccination also played a major role in measles incidence among adults: 53% of cases in adults 20 years of age were in unvaccinated persons for whom vaccine was indicated. Many young adults may have missed immunization during the first years after vaccine licensure, may not have been immunized before the adoption of comprehensive state school laws, or may not have been infected naturally because of declining measles transmission.

In 1989, the number of measlesassociated deaths and the case-fatality rate are higher than in any year since 1971 (CDC, unpublished data). The reason for this increase is not known but could be associated with underreporting of cases, resulting in spuriously high case-fatality rates.

More than half of measles cases occurred among appropriately vaccinated children 5-19 years of age. Primary vaccine failure (rather than waning of vaccine-induced immunity) may be the major reason for the occurrence of measles in this group.5 To reduce the number of primary vaccine failurerelated cases, the Immunization Practices Advisory Committee (ACIP) has recommended a routine two-dose measles vaccine schedule. The initial dose is to be administered to children at 15 months of age, except for children in high-risk areas for preschool transmission, who should be vaccinated at 12 months of age. The second dose is recommended at school entry (4-6 years of age), although localities can choose other ages, such as entry to middle school or junior high school. Both doses should generally be given as measles-mumps-rubella vaccine. In addition, ACIP recommends that colleges and other educational institutions require documentation of two doses of live measles vaccine or other evidence of measles immunity (i.e., prior physician diagnosis or laboratory evidence) for entering students born in or after 1957.

Two approaches to measles control and prevention are crucial until all

localities can fully implement a twodose schedule. The highest priority should always be given to assuring that susceptible persons receive at least one dose of vaccine. In addition, during an outbreak, localities should implement the new outbreak-control recommendations,6 which call for vaccination of all persons at risk (e.g., students attending schools were cases have occurred) who have not received two prior doses and have no other evidence of measles immunity. The ultimate goal, however, will be to implement a routine two-dose schedule in all communities.

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Bacterial Meningitis in Older Children

William A. Bonadio, MD; Mark Mannenbach, MD; Robert Krippendorf, MD

• A review was performed of 25 cases of bacterial meningitis in previously healthy children aged 6 years or older dur-Ing a 10-year period. The rate of infection in this age group relative to all cases of pediatric bacterial meningitis was 4%. Pathogens included Haemophilus influenzae type b in 10 cases (40%), Neisseria meningitidis In 9 cases (36%), and Streptococcus pneumoniae in 6 cases (24%). Physical findings revealed 21 patients (84%) with some degree of altered consciousness and 25 patients (100%) with nuchal rigidity. In all instances, the cerebrospinal fluid exhibited pleocytosis with a predominance of polymorphonuclear leukocytes. Eleven patients (44%) were afebrile on presentation. Of 22 surviving patients, 10 (45%) were afebrile without subsequent fever after administration of the initial dose of antibiotics, in 5 (23%) fever resolved within 24 hours, and in 6 (27%) fever resolved within 48 hours of treatment; there was no instance of prolonged or secondary fever noted. Death occurred in 3 cases (12%). Bacterial meningitis is uncommon in older children. As compared with younger children, older children with bacterial meningitis commonly present without fever and tend to have their fever resolve shortly after effective antibiotic therapy is initiated without manifesting prolonged or secondary fever patterns. Haemophilus Influenzae type b is a common cause of bacterial meningitis in children aged 6 years or older; empirical antibiotic therapy in this clinical situation should include treatment of this path-

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Bacterial meningitis is a serious infection that usually afflicts children younger than 2 years and is uncommon in older children. To our knowledge, there have been no previous studies

performed specifically to characterize the clinical features of older children with bacterial meningitis. The purpose of this study is to characterize the clinical features of children aged 6 years or older with bacterial meningitis.

PATIENTS AND METHODS

A review was performed of the medical records of all cases of bacterial meningitis at the Children's Hospital of Wisconsin, Milwaukee, from 1979 to 1989. Identified were cases involving previously healthy children between the ages of 6 and 18 years. Eliminated from study were those who underwent a prior neurosurgical procedure.

The symptom of altered consciousness was considered present if there was reported lethargy, somnolence, combativeness, disorientation, or seizure activity within 24 hours of admission. At the time of presentation, the triage nurse questioned all caretakers with regard to the current administration of antibiotic or antipyretic medications. Body temperatures were measured every 4 hours during hospitalization, and antipyretic medication was administered on an asneeded basis if fever was documented.

Fever was defined as body temperature above 38°C; prolonged fever was that which lasted for at least 10 days after initiating effective antibiotic therapy; and secondary fever was that which occurred at least 24 hours after 1 complete afebrile day during hospitalization. Normal values of cerebrospinal fluid composition are a leukocyte count of $5\times10^6/L$ or less, glucose concentration of 2.2 mmol/L or more, and protein concentration of 0.40 g/L or less. 1

RESULTS

During the 10-year study period, there were 623 cases of bacterial meningitis; in 81% of cases, the pathogen was Haemophilus influenzae (335 cases), Streptococcus pneumoniae (103 cases), or Neisseria meningitidis (69 cases). In 27 cases, the patient was aged 6 years or older; 2 patients with a ventriculoperitoneal shunt were eliminated from the study.

Of 25 patients studied, the range of ages was 6 to 16 years, with 15 boys and 10 girls; all patients resided in the metropolitan Milwaukee area. The clinical characteristics of these patients are given in the Table. No patient received entibiotics within 72 hours or antipyretics within 4 hours of admission. Cerebrospinal fluid analysis revealed pleocytosis with a predominance (>0.50) of polymorphonuclear cells in all 25 cases. Gram-stained smear of the sediment with pathogenic organisms in 12 cases, hypoglycorrhachia in 11 cases, and abnormally elevated cerebrospinal fluid protein concentration in 15 cases. All patients initially received effective parenteral antibiotic therapy (per the reaults of subsequent susceptibility tests) consisting of ampicillin sodium and 2hloramphenicol succinate; regimens were modified to the use of single agents pased on the results of cultures and susceptibility tests. Of 22 patients who survived, the duration of treatment was at least 10 days. Repeated lumbar puncture was performed in 16 patients within 72 hours of initiating therapy, and all zerebrospinal fluid specimens were sterile. No nosocomial infections were identified.

The causative agents of meningitis in the 11 patients who were afebrile on presentation included *H influenzae* type b (4 patients), *N meningitidis* (4 patients), or *S pneumoniae* (3 patients); those in the 10 patients who were afebrile during hospitalization were *N meningitidis* (5 patients), *H influenzae* type b (3 patients), and *S pneumoniae* (2 patients). Four patients were afebrile on presentation and during hospitalization.

COMMENT

Previous reports cite a considerable decline in the incidence of pediatric bacterial meningitis in children older than 2 years, with over 90% of cases docu-

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Clinical Characteristics*						
Patient Age, y	Neurologic Symptoms	Admission Temperature, °C	Physical Findings	Hospital Temperature Curve	Organism	
13	Headache, neck pain	37.8	NR, petechiae	Afebrile	N meningitidis	
18	Headache, neck pain	37.8	NR, somnolence	Afebrile	N meningitidis	
6	Headache, neck pain	37.0	NR, lethargy	Afebrile in 12 h	HIB	
10	AC	36.6	NR, stupor	Afebrile in 24 h	HIB	
6	Headache, neck pain	37.3	NR, lethargy	Afebrile	HIB	
8†	AC	37.8	NR, coma, shock		S pneumoniae	
8	AC, neck pain	40.0	NR, lethargy, petechiae	Afebrile	N meningitidis	
12	Headache, neck pain	38.8	NR, lethargy	Afebrile in 24 h	HIB	
6	AC	38.6	NR, somnolence	Afebrile	S pneumoniae	
9	Headache, AC	38.8	NR, stupor	Afebrile in 48 h	HIB	
6	Headache, neck pain	36.5	NR, coma, shock, purpura	Afebrile	N meningitidis	
9	Headache, AC	38.4	NR, somnolence	Afebrile	N meningitidis	
6	Headache, neck pain	39.6	NR, lethargy	Afebrile	S pneumoniae	
. 8	Headache, AC, neck pain	38.3	NR	Afebrile	HIB	
16	Headache, neck pain	39.0	NR	Afebrile	HIB	
.14	Headache, AC	36.7	NR, somnolence, shock	Afebrile in 24 h	S pneumoniae	
15	None	36.8	NR, stupor, petechiae	Afebrile in 48 h	N meningitidis	
. 6	Headache, AC	37.4	NR	Afebrile in 48 h	S pneumoníae	
10	Headache, AC, neck pain	37.8	NR, somnolence	Afebrile in 48 h	HIB .	
7†	AC	39.2	NR, stupor, petechiae	•••	N meningitidis	
14	Headache, AC, neck pain	39.1	NR, lethargy	Afebrile in 24 h	N meningitidis	
. 6	Headache, AC	40.4	NR, lethargy	Afebrile in 96 h	N meningitidis	
10	Headache, AC	40.0	NR, lethargy	Afebrile in 48 h	HIB	
6†	Headache, AC	38.7	NR, coma, shock		HIB	
9	Headache, neck pain	39.4	NR, lethargy	Afebril e in 48 h	S pneumoniae	

*NR indicates nuchal rigidity; N meningitidis, Neisseria meningitidis; HIB, Haemophilus influenzae type b; AC, altered consciousness; and S pneumoniae, Streptacoccus pneumoniae. Hospital temperature curve is temperature profile after initiation of antibiotic therapy.

†Died within 48 hours of admission.

mented in those younger than 5 years.²⁵ Our findings are consistent with this, as only 4% of all cases of bacterial meningitis during a 10-year period occurred in those aged 6 years and older. It is also

commonly stated that *H* influenzae meningitis is exclusively a disease of younger children, with 95% of all cases occurring in those younger than 5 years, and is rare in children older than 10

years.²³ Although only 3% of all cases of meningitis due to this pathogen occurred in older children, *H influenzae* type b was the most common cause of bacterial meningitis in our series, accounting for 40% of all cases. Half of all cases of *H influenzae* meningitis in our series occurred in children aged 10 years and older. In light of this, it is important that the range of empirical antibiotic therapy for suspected bacterial meningitis in this age group include treatment for this pathogen.

Neurologic symptoms were commonly experienced by older children with bacterial meningitis. Headache, neck pain, and/or some degree of altered consciousness was reported in all but 1 case. Likewise, some degree of altered consciousness (ranging from lethargy to coma) was exhibited on physical examination by 84% of patients. A prior study⁶ that assessed the frequency of associated nuchal rigidity in children of all ages with bacterial meningitis found that 8 of 16 patients without meningism were older than 2 years, with 3 patients aged 10 years or older. As opposed to this, we found that nuchal rigidity was elicited in every case of bacterial meningitis in older children.

Fever patterns exhibited by older children with bacterial meningitis deviated from that usually described in younger children. Review articles state that fever is an expected finding in older children with bacterial meningitis^{5,7,8}; by contrast, 44% of patients in our series were afebrile on presentation. Of surviving patients, 45% were afebrile without subsequent fever following administration of the initial dose of antibiotics. Prior surveys of children of all ages with bacterial meningitis have shown the common occurrence of both prolonged fever (9% to 13%) and secondary fever (16% to 47%) patterns⁹⁻¹¹; none of these studies specifically distinguished patients by age. In our series, no instance of prolonged or secondary fever occurred. A prior report by Lin et al" found that only 12% of all children with bacterial meningitis were afebrile after 24 hours of antibiotic therapy; by contrast, almost 70% of surviving older children in our series were afebrile without subsequent fever after 24 hours of effective antibiotic therapy.

In accord with the findings of Dodge

and Swartz,¹² coma occurred in 12% of cases and denoted a poor prognosis, as all three of these patients experienced

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shock and two died. The mortality of 12% observed in our series of older children is somewhat higher than the less than 5% rate described for all children aged beyond the neonatal period with bacterial meningitis. 5,12,13-15

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Book Review

Nutrition, Pregnancy, and Early Infancy, by Myron Winick, 182 pp, \$41.95, Baltimore, Md, Williams & Wilkins, 1989.

This book covers the subject of nutrition in the mother during the year before birth and in the child during the year after birth. Dr Winick has done research in nutrition and has edited many books about nutrition; he is well qualified to address the topic. Nutritional needs in the preconception period, during normal pregnancy, and in certain types of abnormal pregnancy, specifically those complicated by adolescence, diabetes, or preeclampsia, are discussed. The subject then shifts to the newborn, both the normal and premature, covering the various topics of breast-feeding, human milk, formula, and mixed feedings. The chapters are organized logically, and the text is very readable. Included are many references to past research, along with some references to research performed in the first half of the most recent decade. Many of the chapters contain summaries and practical suggestions. Some topics are discussed in detail in several different chapters (iron, calcium, and folic acid appear in the chapters on prepregnancy nutrition, vitamins and minerals, and adolescent pregnancy). Current recommended daily dietary allowances are listed most comprehensively in the chapter on adolescent pregnancy.

The pediatric orientation of the author is recognizable in the discussions of *toxemia* (a term used infrequently at present), intrauterine growth retardation (distinguishing between fetal growth problems from vascular insufficiency and fetal growth problems from maternal undernutrition), and gestational diabetes (most authorities do not use insulin to manage gestational diabetes at present). The description of fetal alcohol syndrome (high forehead, prominent cheekbones, and wide epicanthal folds) is unfamiliar. Disturbing are suggestions that women do not realize they are pregnant before organogenesis is complete, and that after birth they need to be told to breast-feed.

Not mentioned are common problems such as early pregnancy nausea, later heartburn, the modern problems of eating disorders, or the energy requirements of women who exercise. Breast-feeding is described as "completing the human reproductive cycle"; the possibility that it would be inappropriate is dismissed, with no discussion of the mother's choice of Lfe-styles or even the possibility of transmission of uncesirable drugs or infections. Total parenteral nutrition in the newborn is not addressed.

In summary, this book covers much of the research that has been done in the area of perinatal nutrition, an area of research in which many health professionals need more background. Medical understanding of the effect nutrition has on the unborn and newborn child is still incomplete. Given the current state of knowledge in the field of nutrition, the text is useful and instructive.

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Newborn Screening for Hemoglobinopathies in Colorado

The First 10 Years

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• In Colorado, newborn screening for hemoglobinopathies by cellulose acetate and citrate agar electrophoresis of dried capillary blood spots was established in 1979. We reviewed the results of screening 528 711 infants through 1988. Fortyseven infants with sickle cell diseases and 27 infants with other hemoglobin diseases were identified. The initial screening failed to detect sickle cell anemia in 4 infants, but the hemoglobinopathy in 3 of these infants was diagnosed correctly by routine retesting of those with suspected sickle cell trait. A total of 47 infants with sickle cell diseases were followed through September 1989. There was no mortality among these infants. The screening test identified 3779 infants (1:140 births) with a suspected hemoglobin trait; confirmatory retesting was obtained in 53%. The results of our experience confirm the value of newborn screening for hemoglobinopathies but suggest that a more sensitive test would improve the program.

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N ewborn screening for sickle cell diseases and other hemoglobinopathies has been advocated for several years, 1-4 and it has recently been recommended for all infants. 5 The primary objective of the early diagnosis of sickle cell disease is to reduce the previously recognized mortality of 8% to 30% from acute complications of overwhelming bacterial infection (sepsis, meningitis, and pneumonia) and splenic sequestra-

tion in the first few years of life. 6-12 Previous studies have shown that this goal can be achieved if early detection of sickle cell disease is linked with a comprehensive program of parental education and medical care that includes the use of prophylactic antibiotics, 12-19 while screening programs without intensive follow-up have had little effect on mortality. 11,20-22 Newborn screening also detects infants with hemoglobin traits and, through testing of other family members, affords an opportunity to identify and counsel couples at risk for having future children with clinically significant disease. 23-28

In 1979, a regional newborn screening program was established in four Rocky Mountain states (Colorado, Arizona, New Mexico, and Wyoming) to test all newborns for hemoglobinopathies and for five other genetic conditions (phenylketonuria, homocystinuria, maple syrup urine disease, galactosemia, and hypothyroidism). Screening tests from the four states were performed in the regional Mountain States Newborn Screening Laboratory at the Colorado Department of Health, Denver, and each state was responsible for its own follow-up procedures. In Colorado, the screening tests were made mandatory by a legislative act in 1981. An important feature of the hemoglobinopathy screening was the routine retesting of infants with hemoglobin traits. We review here the Colorado experience with newborn screering for hemoglobinopathies during the 10-year period from 1979 through 1988 to document the benefits and deficiencies of the program.

SUBJECTS AND METHODS

All infants, regardless of race, were included in the study population. The screen-

ing program was begun in March 1979, and by the end of that year, 40 of the 43 hospital nurseries in Colorado were participating. Approximately 80% of infants born during the first 9 months were tested. After screening was made mandatory in 1981, more than 99% of all infants born in Colorado were tested. A total of 528 711 infants were screened for hemoglobinopathies during the 10-year period.

The cost of laboratory development, laboratory tests, and the follow-up counseling was funded initially by a grant from the US Department of Health and Human Services, Rockville, Md, for the first 3 years. Subsequently, the full cost of the screening tests and partial support for confirmatory testing and counseling have been covered by a minimal charge billed to the families of each newborn by the hospitals in which the screening test was obtained.

Newborn screening was performed on blood obtained by heel stick and applied to a Guthrie paper blotter in the hospital nurseries (or by physicians for home deliveries) and mailed to the Mountain States Newborn Screening Laboratory at the Colorado Department of Health. The same blood sample was used for all six screening tests. Testing for abnormal hemoglobins was performed by hemoglobin electrophoresis by using the two-tier method of Garrick et al.²⁹ Hemoglobin was eluted from the dried blood spots, and all samples were run on acetate strips (Celogram, Helena Laboratories, Beaumont, Tex) at a pH of 8.4. All suspected abnormal samples were then subjected to electrophoresis on citrate agar at a pH of 6.2 (Helena Laboratories). The Mountain States Newborn Screening Laboratory requested a repeated specimen on all unsatisfactory samples. These included blotters with insufficient blood or denatured hemoglobin and tests with only hemoglobin F or with predominantly adult hemoglobin.

The Mountain States Newborn Screening Laboratory reported all abnormal results for Colorado newborns to the Colorado Sickle Cell Treatment and Research Center, Denver, where follow-up procedures were car-

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ried out by a full-time staff member with experience in nursing and genetic counseling. Confirmatory hemoglobin electrophoresis at a pH of 8.4 and a pH of 6.2 was performed in the laboratory of the Colorado Sickle Cell Treatment and Research Center at no charge to the patient. When possible, blood for confirmatory testing was obtained, and counseling was provided by the nurse counselor in the home. Free testing was always offered to family members. Every effort was made to include the appropriate primary health care providers in the follow-up testing and counseling program, and in some cases, the retesting was done in local laboratories.

The race of both parents was requested on the screening form at the onset of the program. It was found on follow-up to be either incomplete or inaccurate in approximately 30% of cases. The data on the racial incidence of hemoglobinopathies in this report include only the infants for whom the diagnosis was confirmed, and for whom the ethnic background of the parents was determined by the sickle cell center counselor or by the primary health care provider after an interview with the mother.

Follow-up data on all infants with a sickle cell disease (SS, SC, and S β -thalassemia) were obtained by a review of sickle cell center clinic records, hospital charts, and direct communication with the primary care physicians. These data include the year 1989 through September for infants born from 1979 through 1988 but only for the period of domicile in Colorado.

RESULTS Newborns With Hemoglobin Diseases

Confirmatory retesting was accomplished on all infants with a presumptive screening pattern of a sickle cell disease. Table 1 lists the diagnosis, number, and incidence of newborns who were identified as having abnormal hemoglobin diseases among the 528 711 infants tested in Colorado from March 1979 through 1988. Homozygous hemoglobin S was the most common disorder with an incidence of 1:13 913 in the total population (1:786 black births). Three infants with SS were born to Arab families. The incidence of all sickle cell diseases (SS, SC, and S β-thalassemia) was 1:10 574 (1:585 in black infants). Homozygous hemoglobin E disease was the next most frequent diagnosis and was found exclusively in southeast Asian infants. A total of 77 or 1:6866 infants were identified as having some homozygous or doubly heterozygous condition.

Sickle cell diseases were diagnosed in a total of 50 patients with sickle cell disease (38 with SS, 10 with SC, and 2 with S β^+ -thalassemia). Three infants with SS left the state before they were 6 months of age. The other 47 infants were followed by the sickle cell center. Thirty-four infants have been observed continuously for a mean period of 4.9 years (range, 1 to 10 years). Thirteen infants moved from Colorado after a mean follow-up of 1.8 years (range, 1 to 3 years). Thus, 47 of 50 infants were followed for 1 year or more to a maximum of 10 years (mean, 4.0 years).

Two episodes of bacterial sepsis due to *Streptococcus pneumoniae* occurred in the 35 patients with SS who were being followed. (One had associated meningitis.) Both recovered with treatment. Ten episodes of splenic sequestration were treated successfully in 7 infants with SS. Two of these episodes occurred in infants at 5 months of age. None of the 47 children with sickle cell diseases have died during the follow-up period in Colorado.

Reliability of Screening Results

False Negatives for Disease. - Table 2 lists the nine false negatives for hemoglobin diseases on the screening test. The correct diagnosis of a hemoglobin disease rather than a trait was made on follow-up retesting in eight of the nine. In one patient with SS, the correct diagnosis was not made until after the first symptoms because routine retesting of presumptive sickle trait had not been accomplished. This infant presented with splenic sequestration at 5 months of age. (Two other infants with SS, not included in Table 2, escaped detection before the onset of symptoms because screening test results were lost through clerical errors, and follow-up was not initiated.) Three of the four infants with SS who were initially reported to have FAS by the screening laboratory were born during a 10-month period in 1986. None of the four infants had received a blood transfusion before testing.

False Positives for Disease.—The 32 false positives for a hemoglobin disease are shown in Table 3. Twenty-sev-

Table 1.—Colorado Newborns With Hgb Diseases*

Disease	No.	Incidence
Homozygous Hgb S	38†	1:13 913
Sickle-Hgb C disease	10	1:52 871
Sickleβ+-thalassemia	2	1:264 356
Sickle-HPFH	2	1:264 356
Homozygous Hgb C	7	1:75 530
Hgb C-β°-thalassemia	2	1:264 356
Hgb C-β+-thalassemia	2	1:264 356
Homozygous Hgb E	11	1:48 065
Hgb E-β°-thalassemia	1	1:528 711
Hgb D-β°-thalassemia	2	1:264 356
Total	77	1:6866

*Hgb indicates hemoglobin; HPFH, hereditary persistence of fetal hemoglobin.

†Includes three cases not detected by newborn sereening and follow-up program.

Table 2.—False Negatives for Disease					
Screening Final Test Diagnosis No.					
FAS	SS	4			
FAC	CC	2			
FAC	C-β+-thalassemia	2			
FAD	D-β°-thalassemia	1*			
Total	• • •	9			

*Blood transfusion given to infant before testing.

en cases were identified by a confirmatory test as a hemoglobin trait, and 5 cases were normal.

Newborns With Abnormal Hemoglobin Traits

On the initial screening, 3779 newborns (1:140) had results that were suggestive of a hemoglobin trait. Confirmafory testing in the sickle cell center laboratory was accomplished in 1996 452.8%). An unknown additional number were tested by the primary physician. A presumptive screening diagnosis of FAS was confirmed in 96.2% of those retested. For FAC, the presumpive diagnosis of a C trait was confirmed in 97.5% of those retested. Suspected raits that did not show FAS or FAC on electrophoresis at both alkaline and acid oH were reported as "unidentified." On retesting, 52.8% were normal, while 23.9% were shown to be typical of hemoglobins D or G, and 13.2% had hemoglo-

Table 3.—False Positives for Disease*					
Screening Test	Final Diagnosis	No.			
FS	AS	8			
FS	AA	1			
F+S>A	AS	4			
F+S>A	AA	2			
FC	AC	5			
FSC	AS	1			
FE	AE	7			
FD or FG	AS	1			
FD or FG	AD or AG	1			
FU	AA	2			
Total		32			

*FI1	indic	ates fo	tal and	unida	ntified	

bin E. Sickle cell trait, C trait, and rare hemoglobin traits constituted the remaining 10.1% of "unidentified" bands. Suspected fast hemoglobin bands were reported separately beginning in 1984, and confirmatory testing was obtained on 121 such infants at a few months of age. Fast bands persisted in 15.7% but had disappeared in 84.3%, suggesting the possibility of Bart's hemoglobin in the majority.³⁰

Table 4 shows the confirmed hemoglobin traits by race. Although the majority occurred in black infants, 23.0% were of other races, and 12.9% of the infants with sickle cell trait were nonblack. The incidence of abnormal hemoglobin traits by race could not be determined since the ethnic background of the families was available only for the infants who were retested.

Table 5 shows the families at risk for future infants with hemoglobin diseases that were identified by follow-up of newborns with an abnormal hemoglobin trait. Only 40 families at risk for an infant with a sickle cell disease were identified.

COMMENT

The primary objective of newborn screening for hemoglobinopathies is the identification of infants with sickle cell disease before the onset of symptoms. This is important because, without newborn screening, mortality from sickle

Table 4.—Confirmed Abnormal Hgb Traits by Race*							
Race Black Spanish White Asian Arab Unknown							
AS	900	73	65	1	3	57	1099
AC	242	18	5	0	0	15	280
AE	1	1	3	66	0	3	74
AD or AG	10	33	73	0	1	10	127
AU	0	1	11	0	0	0	12
AU (fast)	0	3	19	1	0	5	28
Total	1153	129	176	68	4	90	1620

*Hgb indicates hemoglobin; AU, adult and unidentified.

cell disease is greatest during the second 6 months of life. 69 During the 10year period covered by this report, a mandatory statewide screening program identified 47 infants with sickle cell diseases. Three other children with sickle cell anemia escaped early detection and presented with symptoms at 5 to 9 months of age; the possibility that a few others remain unknown to us cannot be excluded. In all, 47 infants with sickle cell disease were referred to a university-based comprehensive sickle cell clinic for care, and 3 moved from the state before referral. None of the children who were so followed up have died, despite the occurrence of numerous lifethreatening complications. Our experience is similar to that of several other reports that demonstrated that early diagnosis, accompanied by prompt referral of affected infants for parental education, prophylactic antibiotics, and comprehensive care, reduces childhood mortality. 12-19 However, mortality data for Colorado children with sickle cell disease born before the advent of newborn screening are not available for comparison. Thus, the number of fatalities averted by our screening and follow-up program cannot be accurately determined.

The detection of infants with asymptomatic hemoglobin traits is a consequence of newborn screening for hemoglobin diseases. The follow-up of such infants provides a unique opportunity to test parents and, thereby, to identify adults with sickle cell disease or couples with hemoglobin traits at risk for having future children with sickle cell disease. In Colorado, a full-time employee of the sickle cell center, skilled in sickle cell

Table 5.—Families at Risk for Future Infants With Hgb Diseases Identified by Follow-up of Newborns With Hgb Trait*

Parents	No.
AS/AS	30
AS/AC	8
AS/S-β-thalassemia	2
AC/AC	1
AC/A-β-thalassemia	. 2
AD/A-β-thalassemia	1
AE/EE	4
AE/AE	1
Total	49

^{*}Hgb indicates hemoglobin.

counseling, was charged with the responsibility to contact mothers, to obtain blood from infants for confirmatory testing, and to test and counsel family members. During the 10-year period covered by this report, these follow-up activities were performed by a registered nurse with roots in the black community. Attempts to contact mothers of infants with abnormal screening tests were made by mail, by telephone, and by visits to homes without telephones. Confirmatory testing of infants and testing of other family members were provided free of charge. If desired by the family, blood was obtained by the nurse counselor in the home. Despite such efforts, and in contrast to the New York experience,24 no parents with previously undiagnosed hemoglobin disease were discovered, and only 40 couples at risk for future children with sickle cell disease were identified. The reasons for this low yield are multiple. Confirmatory testing was accomplished in our laboratory in only 52.8% of infants

whose screening tests indicated a hemoglobin trait. An unknown additional number were tested and counseled by private physicians, but compliance with reporting such results to the sickle cell center was minimal. In many instances, fathers were unavailable or declined testing. Thus, follow-up of infants with sickle cell trait is a costly and somewhat frustrating way to identify and counsel couples at risk for having children with hemoglobin diseases.

Another objective of hemoglobin trait follow-up services is the education of families so that they will be more knowledgeable about hemoglobin traits and not confuse benign carrier states with disease. No data are available to document the degree to which this goal was achieved. One unanticipated benefit of trait follow-up efforts was the identification by confirmatory testing of three infants with homozygous sickle cell disease who had been mistaken for infants with sickle cell trait by the screening test. In addition, the follow-up of sickle cell trait provided interesting information about the ethnic background of infants and highlighted the rather ubiquitous nature of the sickle gene. Of infants with confirmed sickle cell trait, 12.9% were born to families in which neither parent was black.

The value of universal, mandatory screening for hemoglobinopathies has been questioned, 23,81 particularly for states with relatively small black populations. During the study period, 5.2% of infants born in Colorado were black. Previous reports of other newborn screening programs have generally assessed the effectiveness of screening in populations with higher percentages of black infants. For example, the incidence of sickle cell diseases in the recent report by Vichinsky et al¹² was 1:951 newborns who underwent screening. In contrast, the incidence of sickle cell diseases in Colorado was 1:10 574, or 11fold lower. A detailed cost-benefit analysis of screening for hemoglobin diseases in Colorado has not been performed, but the benefits to the 47 infants with sickle cell diseases identified by newborn screening have been considerable. Furthermore, it is noted that even in Colorado, the incidence of sickle cell diseases in newborns was higher than that of four other disorders included in the newborn screening program: phenylketonuria, galactosemia, homocystinuria, and maple syrup urine disease. In addition, the incidence of hemoglobin traits in Colorado was substantial; 1 in 140 screening tests showed a band suspected to be a hemoglobin other than F or A, and a hemoglobin trait was confirmed in 81.2% of those retested.

hemoglobinopathy Theoretically, screening in states with a relatively small-at-risk population would be more cost effective if limited to high-risk ethnic groups, and this possibility had been considered in planning the Colorado screening program. However, targeting certain nurseries was impractical because births of black and Asian infants occur in many hospitals. Selective testing of samples from all hospitals. based on an infant's racial background. would have failed because ethnic data requested on screening test forms proved to be incomplete or inaccurate in about 30% of cases. Furthermore, it was less costly for the screening laboratory to test all filter paper samples for six diseases than to sort some for six tests and others for five. Thus, Colorado's experience supports the recommendation of "universal screening for all newborns for hemoglobinopathies."5

In April 1987, a Consensus Development Panel of the National Institutes of Health concluded that "cellulose acetate followed by citrate agar electrophoresis is the method of choice for large-scale centralized mass screening" for sickle cell disease and other hemoglobinopathies.5 This recommendation was based on data from a number of screening programs that reported generally reliable results with this method. 18,82-34 However. the true incidence of false negatives is unknown, in part, because confirmatory testing of infants with presumed hemoglobin traits has not been routinely performed in most programs. Thus, the information about false negatives has been based mostly on chance identification of older infants with sickle cell diseases who had escaped detection by the newborn screening program. For example, in Cincinnati, Ohio, 3 of 77 infants with sickle cell diseases were identified as having sickle cell trait by newborn screening.17 New York State conducted a limited program of retesting infants

with traits and found 2 infants with homozygous sickle cell anemia and 2 with sickle-β-thalassemia who had been reported to have FAS by a screening test. 4 During the same period, 51 other irfants with sickle cell diseases had been icentified. Our experience was similar: 4 of 50 infants with sickle cell diseases were reported to have FAS by a screening test, and 3 of the 4 were identified correctly by routine retesting. False positives have been found in other programs. 17,34 as well as in Colorado where all infants with a possible hemoglobin disease were retested, and the false positives were identified.

The reasons for the inaccuracies in the screening procedures are not entire-Ly clear. It has been shown that hemoglobin resolution by the screening method used in our laboratory is not as good when using blood spots on filter paper than when using heparinized cap-Hary tube samples35 or cord blood samples. 22,33 The use of the filter paper sample may account for some of our false negatives where an artifact, perhaps the result of sample deterioration during mailing, may have been mistaken for hemoglobin A. In one instance, a prior blood transfusion accounted for the presence of hemoglobin A in an infant with hemoglobin D β°-thalassemia. The observation that three of four false negatives for sickle cell disease occurred during one 10-month period suggests the possibility of human error. Finally, some screening samples may have been mislabeled. This possibility may be the most likely explanation for the infant with FS by a screening test and AA by a confirmatory test. Some false positives for disease may have occurred because technicians were instructed to err on the "safe side" and report hemoglobin A bands only when certain.

Since the development of our screening program, significant advances have been made in hemoglobin testing procedures. Hemoglobin electrophoresis by thin-layer isoelectric focusing 12,30,36,37 and high-performance liquid chromatography have now been adapted for mass screening. Our experience suggests that the accuracy of newborn screening for hemoglobinopathies might be improved by additional quality control efforts and by the use of more sensitive methods. The Mountain

States Newborn Screening Laboratory recently tested 5000 specimens in parallel by both isoelectric focusing and the electrophoretic method (cellulose acetate and agar gel) described in this report. Dried capillary blood on blotter paper provided a satisfactory hemolysate for isoelectric focusing, and the clarity and definition of hemoglobin bands were superior to that obtained by cellulose acetate and citrate agar electrophoresis. Subsequently, on January 1, 1989, the screening laboratory adopt-

ed isoelectric focusing for all future screening. The reliability of this method will be monitored by continued follow-up testing of infants with hemoglobin traits, as well as with disease. We continue to believe that the use of capillary blood on blotter paper remains the most practical sampling procedure for mass screening on a statewide or regional basis, although testing fresh cord blood or heparinized capillary samples may be preferable for selected smaller screening programs.

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The Effect of Postpartum Lactation Counseling on the Duration of Breast-feeding in Low-Income Women

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· We investigated the effectiveness of a program of intensive postpartum support for low-income, breast-feeding women and identified potential predictors of prolonged breast-feeding in this population. Ninety-seven low-income women were randomized to receive intensive postpartum education and support for breastfeeding or to receive only the routine assistance provided by the obstetrical nurses. Both groups were telephoned 6 weeks post partum to determine the method of infant feeding then, and those still breast-feeding were contacted monthly until complete weaning had occurred. No significant difference in breast-feeding duration between the two groups was noted. There was no association between duration of nursing and race, marital status, or the need to return to work or school, Earlier age at Introduction of supplement, younger maternal age, and participation in prenatal classes predicted breast-feeding duration by logistic regression.

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I t is well recognized that breast-feeding is the best form of nutrition for most normal infants.1-4 Although impressive increases in incidence and duration of breast-feeding have occurred in recent years in the United States,5 the greatest increase in breast-feeding has occurred among older, well-educated, more affluent women, and most information in the literature to date has investigated the promotion of breastfeeding among these groups. If the Surgeon General's goals of 75% of infants breast-fed at delivery and 35% at 6 months of age by 19906 are to be met, we must begin to address the problems of breast-feeding promotion among younger, poorly educated, and less affluent groups.

This study was designed to address the following questions. (1) Does intensive postpartum breast-feeding education and support result in a longer duration of breast-feeding among lowincome women? (2) What factors predict a longer duration of breast-feeding in a low-income population?

SUBJECTS AND METHODS

Low-income women who had delivered a full-term healthy newborn at Ohio State University Hospital, Columbus, between March 15, 1986, and January 27, 1987, were eligible for enrollment in this study if they stated an intention to breast-feed when the infant was born. "Low income" was defined as being eligible for Women, Infants, and Children (WIC) program services based on family size and income level. This governmental program provides free nutritional supplement to pregnant and lactating women, children up to the age of 5 years with nutritionally related diagnoses, and infants younger than 12 months old. Although all participants in this study were eligible for WIC, not all enrolled.

Each woman was enrolled in the study during her postpartum stay in the hospital following informed consent as approved by the Human Subject Committee of the university and assigned to either intervention or control groups by random coin toss. If more than one eligible woman occupied the same room, both were assigned to the same group to eliminate contamination of the control group by the educational intervention.

Demographic information for women in the control and intervention groups was obtained by individual interview, while medical information regarding the mothers and their infants was obtained from the medical records. Additional information obtained included postpartum room assignment to routine "rooming-in" vs optional rooming-in (where the mother can choose to have her infant with her or in the nursery), prenatal classes of any type, planned vs unplanned pregnancy, previous attempts to breast-feed other children, whether her mother (ie, the infant's grandmother) had breast-fed her children, and the mother's plans to return to work or school following recovery from delivery. Women were also queried regarding the degree of encouragement to breast-feed they had received from friends and family and their planned duration of breast-feeding.

Women in the control group received only

the routine teaching regarding infant care and feeding usually given by the obstetrical nursing staff on the postpartum floors. Arrangements were made to contact these women again by telephone approximately 6 weeks after delivery.

Each woman in the intervention group was visited by a registered nurse from the Ohio State University Breastfeeding Promotion Project with extensive experience in lactation counseling during her postpartum stay. The nurse spent 30 to 45 minutes with each mother and infant in a one-on-one, bedside teaching session concerning proper breastfeeding techniques, including appropriate latch-on and the use of different positions for nursing. The inappropriateness of supplement and prospective management of some common lactational difficulties were also emphasized. Each intervention group mother was given an easy-to-read booklet entitled Breast Feeding, Baby's Best Start as well as the telephone number of the "Breastfeeding Helpline." This number was connected to an answering machine to ensure round-theclock availability of a nurse or pediatrician from the project to assist with any concerns or questions about breast-feeding.

Intervention group mothers were contacted by one of the project nurses by telephone at 2, 4, and 7 to 10 days and 3 weeks post partum to assist with problems. Specific questions were directed toward difficulties known to occur commonly with lactation at those times. Mothers were reassured that they could reach someone from the project at any time if needed via the telephone helpline. Women experiencing lactation problems that could not be effectively handled via telephone returned to the Lactation Clinic for inperson assistance from the project's nursing and/or medical personnel.

Intervention and control group mothers were contacted at 6 weeks by telephone and questioned regarding current method of feeding, age at weaning and introduction of supplement where applicable, and participation in the WIC program after delivery. Mothers from both groups who were still nursing at the time of the 6-week interview were contacted monthly thereafter until weaning occurred. All infants had been totally weaned by October 1988.

For the purposes of this study, "breast-feeding" or "nursing" is defined as any daily breast-feeding, except where specifically stated. "Bottle feeding" or "weaning" refers to the total absence of breast-feeding.

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Statistical analysis utilized χ^2 analysis, Student's t test, and the Wilcoxon Rank-Sum Test for nonparametric data as well as stepwise logistic regression.

RESULTS In-Hospital Interview

One hundred seventeen women were offered enrollment into the study. Forty-eight women were enrolled into the control group and 49 into the intervention group (Table 1). These numbers would be expected to show a difference in percentage of infants weaned of approximately 20% with $\alpha=.05$ and $\beta=.20$ (one-tailed test). Twenty women (17%) declined to participate, most because they believed they had adequate previous experience and knowledge about breast-feeding.

The participants ranged in age from 16 to 43 years, with a mean of 25.4 years.

Thirteen percent (13/97) were teenage mothers and 54% (52/97) were black. Forty-one percent were married or living with the father, while the remaining 59% were single, divorced, or separated. The majority of families lived in urban areas of Ohio, and their heads of household were largely unemployed, with more than half receiving income only from Welfare or Social Security. Seventy-two percent of women had plans to return to work or school at a mean of 3.5 months after delivery.

This was a first pregnancy for approximately one third of the participants and the second pregnancy in another third; the rest were para 2 or greater. Only 41% were planned pregnancies. More than half of the mothers had begun prenatal care in the first trimester. Approximately one third admitted to at

least occasional use of tobacco and one third had used alcohol, while 3% had used illicit drugs during their pregnancy.

Approximately one third of the women had attended prenatal childbirth classes but none had received specific formal instruction about breast-feeding before delivery. While hospitalized after their delivery, 86% (83/97) reported that they had received bedside instruction from the floor nursing staff and 36% (35/97) had watched a slide show or film about breast-feeding. More than half (55/97) stated that their mothers had breast-fed their children, and only 48% (46/96) had experience with nursing. More than one third (37/92) of the women planned to nurse 6 months or less.

The majority of women had had relatively problem-free pregnancies, and 76% (74/97) had delivered vaginally. Most infants were healthy and of normal birth weight (mean, 3233 g). Six infants were admitted briefly to the neonatal intensive care unit but all were discharged home with their mothers as scheduled. Half (48/97) of the mothers requested and/or were assigned to rooming-in, although in our postpartum units, women are strongly discouraged from keeping their infants through the night. The remainder had optional rooming-in, ie, the infant returned to the nursery at the mother's request at any time during the day.

The χ^2 and Student's t test analyses demonstrated that no significant differences existed between any of these variables and the group assignment.

Postdischarge Follow-up

By the 6-week telephone call, we were unable to contact four control subjects. At least some data were collected on each intervention group subject (Table 2).

Despite the intensity of our postpartum support as an intervention, there was no significant difference in the median duration of breast-feeding between intervention (8.0 weeks) and control (14.75 weeks) groups (Wilcoxon Rank-Sum Test). We had expected to see twice as many intervention group mothers still nursing at 6 weeks compared with controls, but, analyzed by χ^2 techniques, there was no significant difference between intervention and control women in the number still nursing at 6

Variable	Control (n = 4		Interventio (n = 4		P
Maternal age, y	25.1 ± 5.1	(15-37)	24.8 ± 5.6	(15-43)	.8:
Teenage mothers (<20 y)	5	(10)	8	(16)	.6
Race					
В		(60)		(47)	
W		(31).	23	(47)	.2
Other	4	(8)	3	(6)	
Parents living together†	17	(35)	23	(47)	.2
Education <high school<="" td=""><td>12</td><td>(25)</td><td>11</td><td>(22)</td><td></td></high>	12	(25)	11	(22)	
High school	16	(33)	. 24	(49)	.2
>High school	20	(42)	14	(29)	
Source of income (head of household) Unemployed/ADC	32	(67)	25	(51)	٠
Employed (full- or part-time)	16	(33)	24	(49)	.1
Parity	1.2±1.2	(0-5)	1.0 ± 1.0	(0-3)	.3
Prenatal care in 1st trimester	27	(56)	29	(59)	.9
Planned pregnancy	21	(44)	19	(39)	.7
Smoked during pregnancy	17	(35)	16	(33)	.9
Drank alcohol during pregnancy	14	(29)	15	(31)	.9
Used illicit drugs during pregnancy	1	(2)	2	(4)	1.0
Prenatal classes (Lamaze)	19	(40)	16	(33)	.6
Mother's mother breast-fed‡	29/42	(69)	26/47	(55)	.2
Mother previous breast-feeding‡	24	(50)	22/48	(46)	.8
Previous breast-feeding success	15/24	(63)	18/22	(82)	.2
Plans to return work/school‡	34/47	(72)	33/46	(72)	.8.
If so, return <3 mo	17/34	(50)	15/33	(45)	.9
Plan to nurse <6 mo‡	18/44	(41)	19/48	(40)	.4
Cesarean section	. 11	(23)	12	(24)	.7
Assigned to "rooming-in"	25	(52)	23	(47)	.8
Received help from floor nurses	40	(83)	43	(88)	.9

^{*}Data are mean ± SD (range) or number (percent). ADC indicates Aid to Dependent Children. Data were analyzed by χ^2 analysis, except for maternal age and parity. which were analyzed by Student's t test. †Includes legally married and those domiciled together but not legally married.

[‡]Incomplete number because of "do not know" answers.

weeks, at 3 months, and at 6 months. Retrospective assessment of type II error demonstrates that as few as 15 patients in each group would have assured us of not missing a true statistical difference between control and intervention subjects.⁸

Duration of Lactation

The χ^2 analysis was used to test for an association between our demographic and other variables and the type of feeding at 6 weeks (Table 3). The early introduction of supplemental feedings (water, glucose water, formula, or beikost such as juice or cereal) was highly associated with early weaning before 6 weeks; for the infants weaned by 6 weeks, the median age to have received supplement was 1 to 2 weeks, while 45 (31%) of the 55 still nursing at 6 weeks were receiving no supplement at all before 6 weeks. Five women who were still nursing their infants at 6 weeks had already introduced cereal or juice, though none of the weaned infants had received beikost at that age (P = .09). Women who had weaned or introduced formula supplementation were almost twice as likely to be enrolled in the WIC program as those who were still nursing (65% [11/17] vs 33% [22/67]; P = .03).

Other associations with a shorter duration of breast-feeding included later onset of prenatal care, less maternal education, unemployment by head of household, lack of prenatal childbirth education, smoking during pregnancy, and a shorter planned duration of lactation. Contrary to other published data in the literature, we found no association with race, marital status, or the need to return to work or school and the actual duration of nursing.

No difference was noted between early weaners and those still nursing at 6 weeks in their assessment of the encouragement for breast-feeding that they received from the infant's father, their family, or friends. None of the women had utilized La Leche League for assistance.

There were no associations between specific lactation difficulties actually reported to either the nurses in the project or on the postpartum floors and weaning at 6 weeks. However, the most common reason given for weaning at any age was a perceived "lack of supply."

Table 2.—Control vs Intervention Groups: Postdischarge Data* Control Group Intervention Group Variable P (n = 41)(n = 46)13/40 (33) First supplement ≤2 wk 21 (46) .62 Type of supplement Water 8 (20) 8 (17) .95 Formula 13 (32) 10 (22) .42 Juice/cereal 2 (5) 3 (7) .89 Received WIC help post partum 33 (80) 35 (76) .97 Weaned by 6 wk 12/44 (27) 20/49 (41) .25 3 mo 23/44 (52) 32/49 (65) .29 6 ma 34/44 (77) 42/49 (86) .43

^{*}Values are number (percent). WIC indicates Women, Infants, and Children program.

Table 3.—Duration of Lactation*							
Weaned <6 wk Nursing 6 wk							
Variable	(n=3	32)	(n = !	57)	P Value		
Maternal age, y	24.2±5.6	(15-30)	25.3 ± 5.2	(17-37)	.32		
Teenage mothers (<20 y)	5	(16)	8	(14)	.83		
Race B	18	(56)	29	(51) }			
W	13	(41)	23	(40)	.58		
Other	1	(3)	5	(9)			
Parents living together†	12	(38)	25	(44)	.72		
Education <high school<="" td=""><td>14</td><td>(44)</td><td>7</td><td>(12)</td><td></td></high>	14	(44)	7	(12)			
High school	11	(34)	27	(47)	.003		
>High school	7	(22)	23	(40)			
Source of income (head of household) Unemployed/ADC	25	(78)	27	(47)	.009		
Employed (full- or part-time)	7	(22)	30	(53)	.009		
Parity	1.19±1.1	(0-3)	1.01 ± 1.1	(0-5)	.57		
Prenatal care in 1st trimester	12	(38)	38	(67)	.01		
Planned pregnancy	13	(41)	22	(39)	.97		
Smoked during pregnancy	16	(50)	15	(26)	.04		
Crank alcohol during pregnancy	13	(41)	13	(23)	.13		
Used illicit drugs during pregnancy	2	(6)	1	(2)	.61		
Prenatal classes (Lamaze)	5	(16)	27	(47)	.006		
Mother's mother breast-fed‡	21/30	(70)	30/53	(57)	.33		
Mother previous breast-feeding‡	15/30	(50)	23/53	(43)	.73		
Previous breast-feeding success	5/15	(33)	12/23	(52)	.27		
Plans to return work/school‡	19/28	(68)	39/51	(76)	.57		
If so, return <3 mo‡	11/19	(58)	15/38	(39)	.30		
Plan to nurse<6 mo‡	17/31	(55)	16/55	(29)	.03		
Cesarean section	9	(28)	11	(19)	.49		
Assigned to "rooming-in"	21	(66)	26	(46)	.09		
Age at 1st supplement, wk§ ≤2	20	(63)	15/40	(38)			
2-4	11	(34)	13/40	(33) }	.01		
. 4-6	1	(3)	12/40	(30)			

^{*}Data are mean \pm SD (range) or number (percent). ADC indicates Aid to Dependent Children. Data were analyzed by χ^2 analysis, except for maternal age and parity, which were analyzed by Student's t test.

[†]Includes legally married and those domiciled together but not legally married.

[‡]Incomplete number because of missing data. §Excludes 15 exclusively breast-fed infants to avoid bias in favor of a difference between these two groups since, by definition, any infant exclusively breast-fed 6 weeks or longer has not weaned by 6 weeks.

Stepwise logistic regression was used to determine predictors of early (<6 weeks) weaning. Significantly predictive variables, in order of entry into the regression equation, are earlier age at introduction of first supplement (P<.000001), younger maternal age (P<.02), and lack of participation in prenatal classes (P<.03). The ϕ coefficient was equal to .45 with these variables, so that 20.3% of the variance is explained by these three variables.

We reviewed the 87 women for whom we had complete data to determine the percent that our model would have correctly classified in our population. The equation correctly predicted 44 of the 55 mothers still breast-feeding at 6 weeks and 24 of the 32 early weaners. Thus, correct classification occurred in 68 of 87 cases, certainly better than the 50% expected by random classification and significantly (P<.01, χ^2 analysis) better than the 55 of 87 correct that could be achieved by simply predicting all to be still breast-feeding.

COMMENT

Despite an intensive program to educate, assist, and support low-income women to nurse successfully for a prolonged period, we were unable to demonstrate a difference in the duration of lactation between our intervention and control groups. The inability of our regression equation completely to predict the duration of breast-feeding in the women studied suggests that other factors than those we measured were operating as well.

We suspect that, despite our attempts to limit the effect of the intervention among control subjects, there may have been some degree of contamination or Hawthorne effect operation. Certainly, just the presence of our project nurses on the obstetrical floors seems to have stimulated the regular staff's interest in breast-feeding promotion. Although prospectively obtained data are unavailable for a large sample of women delivering at Ohio State University before the onset of our study, a brief retrospective pilot survey of 20 women determined that 50% of these women had weaned by 6 weeks. If this smaller group is, indeed, comparable with our larger prospectively identified group of women, then it appears that our program's interventions may have decreased the rate of early weaning (before 6 weeks) from 50% to 30%, a statistically significant difference (n=97; P<.01).

Perhaps improved postpartum inhospital teaching and encouragement, even though it must be provided during the extremely short maternity stays of the 1980s, coupled with modified hospital regimens, such as elimination of supplement and discharge packs of formula, 9,10 may be sufficient to improve the duration of breast-feeding among mothers motivated at least to attempt breast-feeding. This theory remains to be tested in a prospective study with more control over contamination of control subjects than we were able to achieve in this study.

Many factors had influenced the women in our study that undoubtedly contributed to the overall short duration of lactation. All were eligible for, and 78% participated in, WIC a program that, from many participants' perspectives, rewards bottle feeding over breast-feeding in that the package for bottle feeding includes food for the mother, at least for the first few months, as well as formula for the infant, while "only" the mother receives food if the infant is breast-fed. Lack of true 24-hour rooming-in to allow true demand feeding undoubtedly also had a negative effect on breast-feeding duration. But these effects were equally distributed among subjects in both groups and, therefore, should not have influenced the ability of our intervention to demonstrate a difference in breastfeeding duration between the groups.

Our finding that WIC participation was associated with early formula supplementation or complete weaning contributes to concerns that, in practice, the administration of this program seems to discourage breast-feeding. In 1986 only 13% of WIC infants were breast-fed, and although many WIC sites are beginning to promote breast-feeding actively, statistics documenting an actual increase in breast-feeding at those sites are often not available. 11,12

Little information is available in the literature about the low-income woman who chooses to nurse and even less about those who successfully nurse for a prolonged period. ¹³ Mothers from a private pediatric practice who weaned early shared many characteristics with our

low-income group, including shorter planned duration of breast-feeding and early supplementation with formula. ¹⁴ Our data suggest that low-income women who do nurse for longer than 6 weeks are not characterized by such factors as race, marital status, or previous experience with breast-feeding but may, indeed, in certain characteristics resemble more affluent women who wean late.

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Body Image and Eating Behavior in Adolescent Boys

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· A questionnaire about attitudes toward body weight and shape, and eating and weight control practices, was admin-Istered to 895 adolescent boys. Overall, 42% were dissatisfied with their weight and 33% with their body shape. Sixty-eight percent of the dissatisfied normal weight boys thought they were underweight and 32% thought they were overweight. Sublects dissatisfied with their body shape were most likely to desire an increased chest and arm size and decreased abdomen size. Binge eating (24%) and fasting (12%) were the most prevalent eating practices and were more common in bovs dissatisfied with weight or shape. There was no difference in prevalence of eating practices between boys wishing to gain and boys wishing to lose weight. Although many boys were concerned about body weight and shape, they wished to increase weight and muscularity, rather than lose weight. Blnge eating was common, but was not related to the binge-purge cycle described in girls, because losing weight is not a major concern, and other weight control practices were not more common among boys who wanted to lose weight vs gain.

(AJDC. 1990;144:475-479)

M ost reports of eating disorders have concentrated on unhealthful eating practices and body image concerns in girls. ¹⁻³ Societal and media emphasis on thinness in women appears to be reflected in girls' concern about body weight and shape. It is unclear what effects societal and media influence have on male attitudes toward body

weight and shape. To assess the prevalence of certain eating practices and concerns about their bodies, a large unselected group of adolescent boys was studied cross sectionally to determine their attitudes toward body weight and body shape and prevalence of various weight control practices.

SUBJECTS AND METHODS

The subject population was 895 males aged 12 through 22 years who were seen for health care in a primary-care adolescent clinic at a military medical center between March 1985 and March 1986. The sample was largely middle class, consisting of dependents of active-duty senior commissioned and enlisted military personnel and of retired military personnel now employed as civilians. The sample was predominantly white, with small numbers of black, Hispanic, and Asian subjects.

Subjects' height was measured to the nearest 0.1 cm on a Harpenden stadiometer, and weight was measured in pounds (converted to kilograms) on a standard ballistic scale.

Originally, 1000 anonymous questionnaires that inquired about attitudes toward body weight and shape and whether or not certain eating behaviors had occurred were distributed consecutively. The study population included all who returned questionnaires sufficiently complete for analysis (89.5%). The questionnaire contained 16 questions that were answerable by yes or no. Additionally, subjects were asked to volunteer information, such as amount of desired weight loss or gain, body parts they wished to change, and frequency of eating behaviors, so that these answers would not be biased by suggestion.

The study was approved by the institutional human subjects review board. Written informed consent was not deemed necessary by the institutional human subjects review board, because questionnaires were completed anonymously. Patients were told that the Adolescent Clinic was conducting a survey but that participation was voluntary.

Subject data were organized into three groups based on weight for height and age according to US Department of Health and Human Services tables. 4 Subjects were classified as underweight if their weight was less than the 25th percentile for height and overweight if their weight was greater than the 75th percentile for height. Data were also analyzed by three age groups that roughly corresponded to education level: junior high school (12 through 15 years of age), high school (16 through 18 years of age), and college/career (19 through 22 years of age). Distribution of weight groups was similar among the three age groups ($\chi^2 = 7.4$, P = .11). Statistical analysis was done by computer (IBM PC-AT) using the SPSS program. Data were analyzed descriptively, by analysis of variance or by test of proportions. It is recognized that the use of multiple univariant analyses confers a greater chance of type I error, and this should be kept in mind when interpreting significance, particularly at P<.05.

RESULTS Attitudes Toward Weight

Overall, 42% of the sample were dissatisfied with their current weight. Although only 22% believed that they were overweight, 40% actually were overweight; 18% believed that they were underweight, compared with 11% who actually were. Within weight groups, dissatisfaction with body weight was highest among underweight subjects and in the college/career age group (Table 1).

Of the 135 normal-weight boys who were dissatisfied with their weight, 68% thought that they were underweight and 32% thought that they were overweight. Among 169 overweight boys who were dissatisfied with body weight, 92% believed, correctly, that they were overweight, but 8% thought that they were underweight (data not shown).

A perception of being overweight existed among 196 boys from the top two weight groups; 148 of these wrote down the amount of weight that they wanted to lose. The desired weight loss was

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Table 1.—Satisfaction With Body Weight and Shape and Physical Activity According to Weight and Age*

	No. (%) of Subjects							
	Distribution of Sample	Dissatisfied With Weight	Dissatisfied With Shape	Involved in Sports	Personal Exercise Program	Personal Weight Training		
Weight group Underweight	96 (11)	61 (64)	30 (31)	24 (25)	14 (16)†	13 (14)†		
Normal	441 (49)	135 (31)	119 (27)	205 (47)	74 (17)†	82 (19)		
Overweight :	358 (40)	169 (47)	147 (41)	158 (44)	68 (19)	74 (21)		
Age group JH	402 (45)	152 (38)	115 (29)	210 (52)	42 (10)	49 (12)		
HS	346 (39)	143 (41)	122 (35)	156 (45)	67 (19)	79 (23)		
CC	147 (16)	70 (48)	59 (40)	21 (14)	47 (32)	41 (28)		
Total .	895 (100)	365 (42)	296 (33)	387 (43)	156 (17)	169 (19)		

^{*}JH indicates junior high school; HS, high school; and CC, college/career.

†P<.001 vs overweight.

Table 2.—Perception of Proper Amount of Weight Loss Among Subjects Desiring to Lose, According to Weight

	****	Desired We	ight Loss, No. (%)	of Subjects
	Total No. (%)	Appropriate	Excessive	Insufficient
Weight group Underweight	0	0	0	0
Normal	38	29	9	0
Overweight	110	25	1	84
Total	148 (100)	54 (36)	10 (7)	84 (57)

Table 3.—Body Part Changes Desired by Subjects Who Were Dissatisfied With Body Shape, Depending on Desire to Gain or Lose Weight

		Body	y Part Change De	esired, No. (%)
	No.	Increase in Chest	Increase in Arms	Decrease in Stomach or Waist
Dissatisfied with shape	204	82 (40)	87 (43)	103 (50)
Weight change desired Gain	43	32 (74)	39 (91)	3 (7)
Loss	93	13 (14)	15 (15)	75 (53)
No opinion	68	37 (54)	33 (49)	25 (37)

Table 4.—Involvement in Eating and Weight Loss Behaviors According to Weight and Age*

	-			, % H	laving Tried		
	No.	Diet	Binge Eating	Binge Drinking	Fasting	Self- induced Vomiting	Stimulants
Weight group Underweight	96	0	22	11	11	0	2
Normal	441	4	23	13	12	2 .	. 1
Overweight	358	20	27	17	12	2	2
Age group JH	402	9	20	8	7	1	1
HS	346	11	25	. 15	_, 13	2.	2
CC	147	11	34	30	22	1	3
Total	895	11	24	14	12	2	2

^{*}JH indicates junior high school; HS, high school; and CC, college/career.

appropriate in 36%, excessive (into the underweight category) in 7%, and insufficient (still within the overweight category) in 57% (Table 2). Nine of the 10 who desired an excessive loss were in the normal-weight group, and one was in the overweight group. All of those who desired an insufficient loss were in the overweight group, representing more than three quarters of that group.

Weight and Physical Activity

Only 25% of underweight boys were involved in sports, compared with 47% of normal-weight boys and 44% of overweight boys (Table 1). Of boys not involved in sports, overweight boys were more likely to have a personal exercise program (19%) than normal-weight (17%) or underweight boys (16%) (P < .001). Overweight boys were also more likely to be involved in personal weight training (21%) than were normal-weight (19%) or underweight (14%) boys (P < .001). A smaller proportion of overweight boys who desired an insufficient weight loss were involved in sports (34%) than either the overweight group as a whole (44%) or the entire sample (43%) (P < .001).

Attitudes Toward Body Shape

Of the entire sample, 33% did not like the shape of their body. The greatest prevalence of dissatisfaction with shape was among overweight boys and among the college/career age group (Table 1). Of the 296 who were dissatisfied with their shape, 204 wrote down body parts that they would like to change (Table 3). Decrease in "stomach" or waist was desired by 50%, predominantly among

Table 5.—Involvement in Eating and Weight Loss Behaviors According to Satisfaction With Body Weight and Shape and Desired Weight Change

					%			
	No.	Binge Eating	Binge Drinking	Fasting	Self- induced Vomiting	Stimulants	Involved in Sports	Problem Eating
Body weight Satisfaction	509	19*	11†	9	1	1	46*	7‡
Dissatisfaction	376	31	18	15	2	2	39	17
Body shape Satisfaction	599	20*	13‡	9‡	1	1	45 <u>*</u>	7†
Dissatisfaction	296	33	17	17	3	3	41	19
Desire to change weight Gain	142	30§	. 22,	16	2	2	37	15
Lose	148	32 .	18	17	2	3	38	23
Weight loss desired Appropriate	54	35	15	19	2	4	43	25
Insufficient	84	29	21	13	2	1	35	24
Excessive	10	20	0	40	10	10	40	10

^{*}P vs dissatisfaction. P<.001.

boys who wanted to lose weight. Increases in chest and arms (40% and 43%, respectively) were next most commonly listed. The desire for increased upperbody mass was predominant among boys who wanted to gain weight.

Eating and Weight Control Practices

Overall, 11% had tried a weight loss diet; prevalence increased with weight group but not with age (Table 4). Binge eating had occurred in 24%; prevalence increased by age group and, to a lesser extent, among weight groups. Binge drinking had occurred in 14%, and prevalence increased with both age and weight group. Fasting had been tried by 12%, and there was an increase in prevalence by age group but no difference among weight groups. Self-induced vomiting and stimulant use for weight loss had occurred in 2% and diuretic and laxative use in less than 1%.

Binge eating, binge drinking, and fasting had occurred significantly more often in subjects who were dissatisfied with either their body weight or shape (Table 5). Boys who were dissatisfied with body weight and shape were less likely to be involved in sports (P<.001). There was a slightly higher prevalence of binge eating among boys who wanted

to lose weight, but otherwise there was no significant difference in prevalence of eating or weight control practices between boys who wanted to gain weight and those who wanted to lose weight. Among those who wanted to lose weight, the prevalence of binge eating, binge drinking, fasting, self-induced vomiting, and stimulant use for weight loss was not significantly different in the groups that desired either an appropriate or an insufficient loss. The subjects who desired an excessive loss exhibited a lower prevalence of binge eating and drinking but a higher prevalence of fasting, self-induced vomiting, and stimulant use to lose weight.

There was also a difference in eating behaviors according to which sport a boy tended to be involved in. In four sports there were sufficient participants that analysis could be made of subjects who participated in that one sport to the exclusion of the other three. Binge eating and drinking were most likely to have occurred in basketball players and least likely in soccer players; fasting and self-induced vomiting were most likely to have occurred in wrestlers (data not shown).

Eleven percent of boys thought that they had a problem with eating; this perception was more frequent in boys who were dissatisfied with body weight (P<.05) or shape (P<.01) (Table 5). When compared with the entire study population, a higher proportion of boys involved in the reported eating practices believed that they had a problem with eating—18% of those who had experienced binge eating, 22% of those who had fasted, and 29% of those who had experienced self-induced vomiting or used stimulants.

COMMENT

Less than half of all boys were dissatisfied with their weight. This is in contrast to a similar group of adolescent girls, two thirds of whom were dissatisfied with their weight.3 Even among overweight males who perceived, correctly, that they were overweight, more than three quarters did not desire sufficient weight loss to enter the normal-weight range. It is possible that the boys desiring insufficient loss were heavy because of increased muscularity and perceived that appropriate weight would result in a loss of either attractiveness or athletic ability. The latter explanation is unlikely, because fewer of this group were involved in sports than the rest of the overweight group. It is more likely that they were just not weight conscious and were not aware of

[†]P vs dissatisfaction. P<.01.

[‡]P vs dissatisfaction. P<.05.

[§]P vs lose. P<.01.

appropriate weight ranges for their age.

Rather than a preoccupation to become thin, as is seen in girls, there was more concern among boys about being too thin. The fact that fewer underweight than normal-weight boys were involved in sports suggests an athletic selection bias against underweight boys that might explain an increased tendency for even normal-weight boys to want to gain weight, particularly if increased weight were equated in their minds with increased muscularity. Although differences in pubertal maturation could be invoked to explain the low involvement of underweight boys in sports, these subjects are underweight for height, not necessarily underweight and short, as is characteristic of boys with delayed puberty.

Even among normal-weight boys who were dissatisfied with their weight, more than twice as many wished to gain weight as to lose weight. This finding is in contrast to a group of normal-weight adolescent girls, wherein a majority wished to lose weight, and agrees with an earlier study that found that high school boys had a tendency to view themselves as too thin or underweight.

Dissatisfaction with body shape was less prevalent than dissatisfaction with weight, but overweight and older boys were more likely to be dissatisfied with their shape. Increase of body shape dissatisfaction with age may be related to longer exposure to societal and media ideals of male body shape. The most common change sought was decrease in "stomach" and waist size, primarily in overweight boys. This concern may reflect a growing societal preference for flat abdomens and "hard" bodies. Increase in upper-body size was also a predominant change sought, regardless of whether the boy was underweight, of normal weight, or overweight. This probably reflects a male ideal that equates attractiveness and esteem with the appearance of strength and prominent pectoralis and biceps muscles.6

Dieting was not common in boys. This finding is consistent with a decreased concern with being overweight and is similar to the finding that only 5% of English teenage boys were dieting. Another possible explanation for the decreased prevalence of dieting by over-

weight boys is that boys who wish to lose weight may be more likely to exercise than to diet. Supporting this view is the finding that a greater percentage of overweight than normal or underweight boys were involved in personal exercise and weight training programs. If such personal programs are intended to increase muscle mass, they may place these boys at risk for use of anabolic steroids.

Fasting, self-induced vomiting, and stimulant use, which are commonly associated with weight control in girls. were uncommon in boys, confirming that weight loss is not a sufficiently important concern in boys to warrant the use of these methods. Rather, being underweight and underdeveloped was more of a concern. Binge eating had occurred in a quarter of the boys, somewhat more than the 18% of Irish college males reported in one study, but its prevalence was not correlated with weight, and it appeared not to be related to weight control. Binge eating was more common among boys who were dissatisfied with their weight or shape, and slightly more so among boys who wanted to lose weight, but it did not appear to be linked to other weight control practices. The lack of correlation between binge eating and a binge-purge cycle is supported by the finding that the 10 boys with a desire for excessive weight loss did not have an increased prevalence of binge eating, although there was an increased prevalence of self-induced vomiting, fasting, and stimulant use.

Although most adolescent boys did not tend to be preoccupied with eating or weight loss, they were more likely to believe that they had a "problem" with eating if they were dissatisfied with body weight or shape or if they had indulged in binge eating, fasting, or selfinduced vomiting. This finding may indicate that adolescent boys who are dissatisfied with their weight or shape are more critical of their dietary intake and that they regard fasting, self-induced vomiting, and even binge eating as aberrant practices, even though these practices are not correlated with desire for weight loss.

There may be a subgroup of boys for whom perception of weight and shape is related to unhealthful weight control practices. The ten boys who desired an excessive weight loss had an increased prevalence of fasting, self-induced vomiting, and stimulant use but were less likely to believe that they had a problem with eating. This pattern of weight control practices and attitudes suggests a preoccupation with weight loss similar to that seen more commonly in girls.3 The number in this group is too small to draw a conclusion, but there may be selected boys, identifiable by an appropriate screening questionnaire, who are at risk for developing unhealthful practices to lose weight or to avoid gaining weight.

The increased prevalence of binge eating in basketball players may reflect a need for taller athletes to eat more or to "bulk up" more. The increase in binge drinking could be related to an increased social status enjoyed by taller boys. The small size of soccer players would confer a lesser social status and could explain the lower prevalence of binge drinking.

Wrestlers, who generally are thought to be extremely weight conscious, were more likely to have participated in binge eating than football or soccer players. They were also more likely to have attempted fasting, an attitude of restraint from eating also noted in a study of American wrestlers, skiers, and swimmers. Since administration of the questionnaire was not controlled for active participation in the sport, it is unknown whether the binge eating took place during or outside of the wrestling season.

The generalizability of this study bears comment. Although blacks are overrepresented and Hispanics are underrepresented in the US Army compared with the US population, the ethnic composition of this study population is closer to the population norm than studies of inner-city youth or suburban high school youth, for example. Because military families in the volunteer army are drawn from all over the country, this study does not suffer from a regional bias. Although least and most wealthy subjects are underrepresented, it is socioeconomically representative of the majority of the US population. The composition of the sample does have a military bias, although many of the adolescents' parents were civilians

at the time of the study. It is unknown whether military adolescents have different attitudes than others.

CONCLUSION

Several conclusions may be drawn from this study. First, although a significant number of adolescent boys, like adolescent girls, are dissatisfied with current weight or body shape, their concern centers around not wanting to be

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underweight and wanting to increase upper-body mass.

Second, adolescent males are not greatly involved in weight loss practices, even when they are overweight. There may be individuals, however, who are indulging in unhealthful practices to gain or lose weight, and it may be possible to identify these with a few questions about satisfaction with current weight and body shape as well as

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eating and exercise activities. Third, binge eating by adolescent males appears to be more a "variant" adolescent eating behavior than part of a binge-purge cycle related to weight control, as may be the case in adolescent gris. Finally, further study of the eating practices of adolescent athletes may permit identification of problem eating practices associated with specific sports.

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Book Review

Chronic Illness During Childhood and Adolescence: Psychological Aspects, by W. T. Garrison and S. McQuiston, 160 pp, \$19.95, Newbury Park, Calir, Sage Publications, 1989.

Chronic Illness During Childhood and Adolescence: Psychological Aspects is a well-written and concise monograph from the Sage series, summarizing the current knowledge of the field. The Sage Series in Developmental Clinical Psychology and Psychiatry addresses a variety of topics from a multidisciplinary viewpoint, focusing on contemporary theory and research. The material covered in this work is most relevant to health care providers in pediatrics, child psychology, child psychiatry, nursing, and social work.

The monograph begins with a series of case vignettes, accompanied by individual commentaries. The cases chosen for discussion illustrate common and often frustrating problems encountered in the care of children with chronic diseases. The commentaries are thoughtful and thought provoking.

An overview of childhood chronic diseases is provided in the second section, beginning with a historical perspective and contemporary incidence and prevalence patterns. More specific information concerning prevalence, incidence, natural history, and developmental and psychological correlates are provided for 13 disease categories. These diseases include juvenile rheumatoid arthritis, asthma, chronic renal failure, congenital heart disease, cystic fibrosis, diabetes mellitus, hemophilia, childhood cancer, neuromuscular disease, acquired immunodeficiency syndrome, sickle

cell disease, seizure cisorders, and spina bifida.

The third and fourth sections are devoted to an in-depth analysis of the impact of chronic illness on development and psychosocial functioning. Topics addressed include children's concepts of health and illness, cognitive functioning and academic performance, stress, and coping with chronic illness.

The last section addresses clinical intervention methods. The most commonly employed techniques are described, and their theoretical strengths and weaknesses are highlighted. Once again, case studies are used to illustrate concepts. The monograph ends with a short commentary outlining the obstacles to clinical and research progress and a framework for future research.

This monograph has several strengths, the foremost its firm foundation in clinical research. Drs Garrison and McQuiston have reviewed an extensive amount of literature and have succinctly summarized the material into a work of 160 pages. The topics included are germane to clinical practice. I would recommend this monograph to any professional interested in the psychological and developmental aspects of childhood chronic illness.

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The Humoral Immune Response to Type 1 Oral Poliovirus Vaccine in Children Previously Immunized With Enhanced Potency Inactivated Poliovirus Vaccine or Live Oral Poliovirus Vaccine

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 Sixty-one children who had previously received three doses of enhanced potency inactivated policylrus vaccine (epIPV) at 2, 4, and 18 months of age and 56 children who had previously received oral poliovirus vaccine (OPV) according to the same schedule were challenged with a single dose of monovalent, type 1 oral poliovirus vaccine (OPV1) between 19 and 52 months of age. Before the OPV1 challenge, the previously epiPV-immunized recipients had a geometric mean poliovirus type 1 microneutralization antibody titer (geometric mean titer [GMT]) of 11.1 IU, which was significantly higher than the prechallenge GMT of 2.2 IU among the children who had previously received OPV. Three weeks after the OPV1 challenge, the GMTs for the epiPV-immunized recipients and the OPV-immunized recipients were 35.3 IU and 5.1 IU, respectively. For the epIPV-immunized recipients, both the prechallenge GMT and the postchallenge GMT were dependent on

the D antigen content of the vaccine that they had previously received. A fourfold or greater rise In poliovirus type 1 antibody occurred after the OPV1 challenge in 50.9% of the epiPV-immunized children and in 28.6% of the OPV-immunized children; this difference was statistically significant. For both groups, antibody boosts were inversely correlated with the prechallenge serum antibody titer. However. the epiPV-immunized children consistently were more likely to boost than the OPVimmunized children at equivalent levels of prechallenge antibody. This experience Indicated that OPV1 administration effectively raises the level of serum antibody in children previously immunized with three doses of epiPV, especially in children with lower levels of preexisting antibody. This booster response was superior to the booster response of children who received three doses of OPV.

(AJDC, 1990;144:480-484)

A lthough paralytic poliomyelitis has been successfully controlled in the United States, there is still controversy over the relative merits of live, attenuated oral poliovirus vaccine (OPV) and inactivated poliovirus vaccine (IPV).

Poliomyelitis vaccine public policy is currently undergoing reanalysis1 because the rare cases of paralytic poliomyelitis that are now occurring are mostly caused by live vaccine polioviruses, and also because of the introduction and recent licensure of enhanced potency inactivated poliovirus vaccines (epIPVs) that are more immunogenic than the standard inactivated vaccines previously available in the United States.^{8,4} One policy option under consideration is the sequential use of epIPV and OPV as an alternative to the exclusive use of either vaccine. 1,5 There is little information regarding the serologic response to OPV among children previously immunized exclusively with IPV. 6,7 To our knowledge, there are no published studies of the OPV booster response among children previously immunized with the recently developed epIPV preparations.

From March 1985 to June 1986, we conducted a study to compare the intestinal immunity conferred by epIPV and OPV. The design of this study also allowed an evaluation of the humoral immune response following type 1 OPV administration to a group of children previously primed by either three doses of epIPV or three doses of OPV.

SUBJECTS AND METHODS Participants

Children between the ages of 19 and 52 months were recruited from a public health clinic and from a private practice in suburban Maryland. Children were excluded if they had been exposed in the household to siblings who had received OPV or would receive OPV during the course of the study. They were also excluded if they had attended day care for more than 120 child-days. The number of child-days was defined as the number of children in the immediate care group times the number of days attended per week times the number of weeks attended in the child's lifetime.

One cohort of children had previously participated in clinical trials of three investigational, enhanced potency trivalent inactivated poliovirus vaccines: Connaught Laboratories Human Diploid Cell (CHD) vaccine, Connaught Laboratories Monkey Kidney Cell (CMK) vaccine, and Merieux Institute Monkey Kidney Cell (MMK) vaccine. The respective D antigen content for type 1 poliovirus (PV1) was 53, 25, and 24 U per dose for these three preparations. These children received three doses of the investigational epIPV at 2, 4, and 18 months of age and then received the challenge dose of type 1 OPV between 19 and 47 months of age.

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The second cohort of children had previously received three doses of licensed trivalent OPV at 2, 4, and 18 months of age, as verified by clinic records. These children were challenged with type 1 OPV between 19 and 52 months of age.

Study Design

After informed consent was obtained, a serum specimen was obtained, and every participant was fed a single dose of monovalent, oral policyirus vaccine that contained an 800 000 median tissue culture infective dose (TCID, o) of attenuated type 1 poliovirus per 0.5 mL. This dose was equivalent to the type 1 OPV content of trivalent, oral poliovirus vaccine licensed for use in the United States. A second serum specimen was obtained from each participant 3 weeks after the type 1 CPV challenge.

Laboratory Methods

Serum specimens were tested for type 1 poliovirus antibody by a standard microneutralization method by using Mahoney strain type 1 poliovirus and cultured Vero cells. Antibody titers were determined to be the reciprocal of the highest dilution of serum that neutralized between 30 and 80 median tissue culture infective doses of virus. Many serum specimens had a neutralizing activity at the highest dilution tested that varied between 1:5786 and 1:92 576 before conversion to international units. There was an insufficient amount of serum that remained from some of these specimens to determine an end point by repeated testing. The titer assigned to these sera is the highest tested, but the actual titer may be higher.

A standard reference serum (World Health Organization International Standard for Antipoliovirus Sera, Statens Seruminstitut, Copenhagen, Denmark) was included in each batch of microneutralization assays. The antibody titer observed for the standard serum was used to convert the microneutralization titers to international units of poliovirus antibody.

Statistical Methods

Student's t test was used to analyze the variances of means, and the χ^2 test was applied to the analysis of variances of proportions.

RESULTS

The epIPV cohort consisted of 61 children who were aged 19 to 47 months on entry into the study. Thirty of these children had previously received the CHD vaccine, 19 had received the CMK vaccine, and 12 had received the MMK vaccine. The 56 OPV-immunized chil-

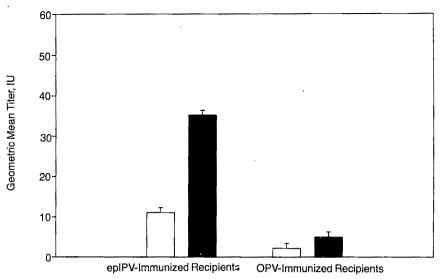


Fig 1. — Geometric mean poliovirus type 1 antibody titers (international units) before (open bars) and 3 weeks after (closed bars) administration of monovalent, oral poliovirus type 1 vaccine (OPV1). Enhanced potency inactivated poliovirus vaccine (EpIPV)-immunized children had previously received three doses of enhanced potency inactivated poliovirus vaccine. OPV1immunized recipents had previously received three doses of OPV1. Bars indicate SEM.

3		Dilution Tested*	9,
	No.	Prechallenge Sera	Postchallenge Sera
epiPV-immunized	61	R	18

Table 1.—Number of Sera-Neutralizing Type J Polioviruses (Reaching an End Point)

	No.	Prechallenge Sera	Postchallenge Sera
epIPV-immunized recipients, total	61	8	18
CHD	30	7	16
CMK	19	0	0
ММК	12	1	2
OPV-immunized recipients	56	1	3

ep!PV indicates enhanced potency inactivated poliovirus vaccine; CHD, Connaught Laboratories Human Diploid Cell vaccine; CMK, Connaught Laboratories Monkey Kidney Cell vaccine; MMK, Merieux Institute Monkey Kidney Cell vaccine; and OPV, oral poliovirus vaccine.

dren were aged 19 to 52 months on entry into the study. The mean age of the epIPV cohort (26.6 months) was similar to the mean age of the OPV cohort (28.3 months) when challenged with monovalent, type 1 oral poliovirus vaccine (OPV1) at entry into the study. The mean interval between the third dose of epIPV for the first cohort and the third dose of OPV for the second cohort and subsequent OPV type 1 challenge was 6.8 months and 8.1 months, respectively.

Figure 1 illustrates the geometric mean poliovirus type 1 antibody titers (geometric mean titers [GMTs]) for sera drawn from the epIPV-immunized recipients and the OPV-immunized recipients on the day of OPV1 challenge and weeks after challenge. The prechallenge GMT for the epIPV-immunized children (11.1 IU) was significantly higher than the prechallenge GMT for the OPV-immunized children (2.2 IU) P<.0001). Three weeks after the OPV1 administration, the GMT for the epIPV-immunized recipients was 35.3 IU, a 3.2-fold increase over the prechallenge GMT. This postchallenge antibody response for the epIPV-immunized children was significantly greater than that for the OPV-immunized chil-Firen who experienced a 2.3-fold rise to 5.1 IU (P<.0001). These differences for

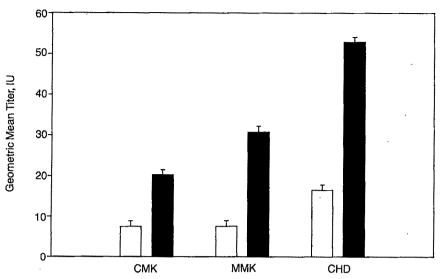


Fig 2.—Geometric mean poliovirus type 1 antibody titers (international units) before (open bars) and 3 weeks after (closed bars) administration of monovalent, oral poliovirus type 1 vaccine to enhanced potency inactivated poliovirus—immunized children, according to the type of enhanced potency inactivated poliovirus vaccine that they had previously received. CMK indicates Connaught Laboratories Monkey Kidney Cell vaccine; MMK, Merieux Institute Monkey Kidney Cell vaccine; CHD, Connaught Laboratories Human Diploid Cell vaccine; and bars, SEM.

both prechallenge and postchallenge GMTs between the epIPV-immunized recipients and the OPV-immunized recipients were minimum differences, since the proportion of sera from the epIPV-immunized recipients that did not neutralize type 1 poliovirus at the highest dilution tested was higher than for sera from the OPV-immunized recipients (Table 1).

Figure 2 illustrates the prechallenge and postchallenge GMTs for the recipients of the different epIPV vaccines. Recipients of each of the three epIPV vaccines had significantly higher prechallenge GMTs and significantly higher postchallenge GMTs than OPVimmunized children. Children who received three doses of the CHD vaccine, ie, the vaccine with the highest type 1 poliovirus D antigen content, had a higher prechallenge GMT (16.5 IU) than recipients with either the CMK vaccine (7.5 IU) or the MMK vaccine (7.6 IU), but the differences were not statistically significant. Three weeks after OPV1 challenge, the CHD-vaccinated recipients had a GMT of 52.9 IU that was significantly higher than the postchallenge GMT for the recipients of the CMK vaccine (P = .003), but not for the recipients of the MMK vaccine (P=.17). Since the CHD-vaccinated recipients had a high proportion of prechallenge and postchallenge sera that did not neutralize poliovirus type 1 (PV1) at the highest dilution (Table 1), then the differences observed between the GMTs associated with this vaccine and the GMTs associated with the other vaccines must be considered minimum differences. The true differences were probably greater.

A booster response was defined as a fourfold or greater increase in the serum antibody level after OPV1 challenge. Booster responses could not be evaluated for eight participants because of either prechallenge or postchallenge sera that did not neutralize at the highest dilution tested. These eight children were all CHD epIPV-immunized recipients. They had been excluded from the following analysis of booster responses, although their exclusion did not alter the study's conclusions in any way.

As shown in Table 2, 50.9% of epIPV-immunized children experienced a boost in antibody titer, significantly more than the 28.6% of OPV-immunized children who had a fourfold or greater rise (P=.016). There was no obvious difference in the proportion of children with boosts among recipients of the various epIPVs, but the ability to demonstrate differences of statistical

Table 2.—Proportion of Children
Experiencing a Fourfold Rise in PV1
Antibody Titer After OPV1
Challenge*

	No.	No. (%) of Boosts
epIPV-immunized		
recipients, total	53	27 (50.9)
CHD	22	11 (50.0)
CMK	19	9 (47.4)
MMK OPV-immunized	12	7 (58.3)
recipients	56	16 (28.6)

*PV1 indicates poliovirus type 1; OPV1, oral poliovirus vaccine type 1; epIPV, enhanced potency inactivated poliovirus vaccine; CHD, Connaught Laboratories Human Diploid Cell vaccine; CMK, Connaught Laboratories Monkey Kidney Cell vaccine; MMK, Merieux Institute Monkey Kidney Cell vaccine; and OPV, oral poliovirus vaccine.

significance was limited by the small number of children in each group and by the lack of neutralization end point data for some of the participants (Table 1).

For both experimental groups, antibody boosts were inversely related to the prechallenge antibody titer. When children were stratified according to the prechallenge titer, those with the lowest prechallenge titers were most likely to experience a booster response to OPV1 challenge (Table 3). Higher levels of prechallenge antibody were associated with a lower rate of booster responses. However, at each level of prechallenge antibody, epIPV-immunized children were more likely to boost than OPV-immunized children (by the χ^2 test, P = .10, .0003, and .076 for antibody titer ranges of <1.0 IU, 1 through 10 IU, and >10 IU, respectively).

For both study groups, the magnitude of the antibody rise was greater for children with low prechallenge titers than children with high prechallenge titers. Figure 3 illustrates the mean fold rise or fall of PV1 antibody for children, stratified according to the prechallenge antibody titer. Prior epIPV-immunized recipients and prior OPV-immunized recipients with a titer of less than 1 IU had a mean rise in the antibody titer after OPV1 challenge of 74 fold and 56 fold, respectively, ie, a difference that was not statistically significant. However, there was a significant difference (P=.03) between the two study groups in the fold increase for the stra-

Table 3.—Proportion of Children Experiencing a Fourfold Rise in PV1 Antibody Titer
After OPV1 Challenge According to Prechallenge Antibody Titer*

Group	No.	No. (%) of Boosts
epIPV	. 4	4 (100.0)
OPV	14	8 (57.1)
epIPV	18	14 (77.8)
OPV	35	8 (22.9)
epIPV	31	10 (32.3)
OPV	7	0 (0.0)
	epiPV OPV epiPV OPV epiPV	epIPV 4 OPV 14 epIPV 18 OPV 35 epIPV 31

*PV1 indicates poliovirus type 1; OPV1, oral poliovirus vaccine type 1; epIPV, enhanced potency inactivated poliovirus vaccine; and OPV, oral poliovirus vaccine.

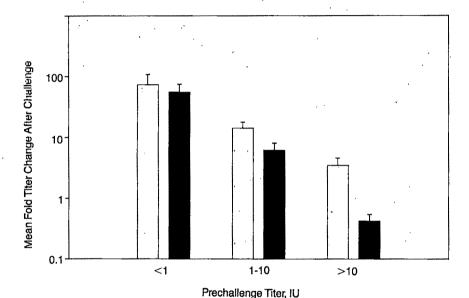


Fig 3.—Mean fold change in poliovirus type 1 antibody titer among both experimental groups, according to prechallenge antibody titer. The *y* axis is logarithmic. Changes of less than 1.0 represent a decrease in antibody titer. Bars indicate SEM; open bars, recipients of enhanced potency inactivated poliovirus vaccine; and closed bars, recipients of oral poliovirus vaccine.

tum with prechallenge antibody titers of 1 through 10 IU. None of the seven OPV-immunized children with prechallenge antibody titers of 10.0 IU or more experienced a fourfold rise in titer after challenge (Table 3), and the mean titer for these children actually fell to 42% of the prechallenge mean titer after OPV1 challenge (Fig 3). In contrast, 10 (32.3%) of the 31 epIPV-immunized children with prechallenge antibody titers of greater than 10 IU experienced a fourfold rise, and overall, this group had a mean titer rise of 4.0 fold.

COMMENT

Millions of US children who were previously vaccinated with the original

Salk IPV received OPV in the early 1960s shortly after OPV was licensed. From 1962 to 1964, 62% of 1- to 4-yearold children and 82% of 5- to 9-year-old children had received three or more doses of IPV before they received OPV.10 Passive surveillance indicated no untoward effects of such sequencing of vaccines, but little information was obtained with regard to immunogenicity following administration of successive IPV and OPV vaccines. A study of IPV-immunized schoolchildren in Ontario, Canada, found that those children who received OPV during a single mass campaign in 1962 were significantly more likely to possess antibodies to all three poliovirus types in 1969 and 1970

than did children who received IPV alone." These data indicated that a singie dose of OPV enhanced serum antibody persistence among children who received the conventional IPV as infents. More recently, Ogra6 and Dhar and Ogra7 showed that a single dose of CPV given at 12 months of age to a small number of infants, who previously received three doses of conventional IPV at 2, 3, and 4 months of age, boosted serum PV1-neutralizing antibody to higher levels than achieved in infants who had previously received three doses of OPV. The IPV-primed infants a so produced higher levels of nasopharyngeal anti-PV1 IgA after the OPV booster than infants primed with three dioses of OPV.

Our data address the humoral immune response following a single TCIDs of 800 000 of type 1 OPV among children who have previously received either three doses of epIPV or three coses of OPV according to the currently recommended vaccine schedule.12 When CPV is administered from 1 to 34 months after the primary series of either vaccine, children previously vaccirated with epIPV are more likely to undergo a booster response and to experience considerably higher titers of PV1 antibody than children previously vaccirated with OPV. Furthermore, booster responses are more likely to occur in prior epIPV-immunized recipients than in prior OPV-immunized recipients who possess equivalent levels of prechallenge PV1 antibody.

Thus, one dose of type 1 OPV effectively boosts serum-neutralizing antibody in children previously primed by EDIPV. This superior response probably results from enhanced replication of the OPV challenge virus in the gastrointestinal tract in epIPV-immunized children with lower local immunity, thus allowing a greater antigenic stimulus of the immune system that has been previously primed by epIPV.8 Conversely, OPV-immunized recipients do not boost as readily because rep-Ecation of the OPV challenge virus is inhibited by previously induced secretory immunity.8

If trivalent OPV is shown to induce a similar reponse to all three serotypes among children previously given two or more doses of epIPV, then a sequential

epIPV-OPV schedule should prove to be a highly effective regimen that produces high titers of poliovirus antibody. A high titer of poliovirus antibody does not necessarily confer superior immunity since virtually any detectable neutralizing antibody is thought to provide protection against paralytic disease. Infants who experience seroconversion with either vaccine may be protected for many years. Virtually 100% of infants

who receive two doses of epIPV at 2 and 4 months of age and 90% to 100% of infants who receive two doses of OPV at the same ages have antibody to all three poliovirus serotypes. Thus, both vaccines provide humoral immunity against poliomyelitis. However, oral and inactivated vaccines provide different degrees of gastrointestinal secretory immunity. The degree to which a sequential epIPV-OPV schedule will

provide local immunity equal to the currently recommended OPV schedule is not known. Furthermore, the relative importance of secretory immunity in the control of poliomyelitis is subject to debate. Additional investigation is needed to assess all aspects of immunity before the optimal sequential epIPV-OPV immunization schedule can be determined.

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CORRECTION

Missing Units of Measure.—In the article entitled "Nonphenylketonuric Hyperphenylalaninemia" published in the December 1989 issue of AJDC (1989;143:1464-1466), information was incomplete in one of the tables. In the second column of Table 1, "Pheny" indicates phenylalanine and the values, given in milligrams per deciliter, are of levels taken at the time of the examination. The brace indicating Wechsler Scales should have been over IQ scales only and should not have included readings of phenylalanine levels.

Pregnancies in Human Immunodeficiency Virus-Infected Sex Partners of Hemophilic Men

Janine Jason, MD; Bruce L. Evatt, MD; The Hemophilia-AIDS Collaborative Study Group

· We investigated 24 completed pregnancies of 20 healthy, human immunodeficiency virus (HIV)-seropositive sex partners of 20 seropositive hemophilic men. One woman had recurrent herpes simplex type 2 infection; no woman was known to use illicit drugs or to have other purported cofactors for vertical HIV transmission. For 8 offspring, the mothers learned of their partners' serostatus and received counseling against pregnancy prior to the fifth month of gestation; for 9 offspring (37.5%), the mothers learned of their own seropositivity and received counseling prior to the fifth month. Acquired immunodeficiency syndrome developed in 7 (35%) of 20 fathers, 4 of whom died; HIV-related symptoms developed in 4; severe liver disease developed in 2; and 7 (35%) were in good health. In four mothers (20%) HIVrelated symptoms developed. Five offspring were breast-fed for 2 days to more than 3 years, two while the mother was known to be seropositive; four of these were seronegative and healthy, and one was seropositive at 30 months of age and had persistent cervical lymphadenopathy at 48 months of age. Infants were born at term; median birth weight was 2.86 kg. Solely on the basis of serologic studies and symptoms for those with more than 15 months of follow-up, the minimum perinatal transmission rate for this group of women without putative transmission cofactors (drug usage, promiscuity, malnutrition, HIV symptoms) was at least 25%, a rate comparable to that reported for women in other risk groups.

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In March 1987, the Centers for Disease Control, Atlanta, Ga, in cooperation with the National Hemophilia Foundation (NHF), conducted a survey of all US hemophilia treatment centers (HTCs) and physicians known to treat patients with hemophilia to determine (1) whether sex partners of hemophilic men known to be infected with human immunodeficiency virus (HIV) were being tested for HIV antibody. (2) the HIV seroprevalence rate among partners being tested, and (3) the extent of compliance with the NHF and Public Health Service guidance and recommendations for preventing sexual and perinatal transmission of HIV.2-10 Two hundred thirty-seven (96%) of the 246 health care providers contacted responded, reporting on 2276 spouses/sex partners of a comparable number of known HIV-seropositive hemophilic patients. Despite recommendations against un-protected intercourse by and with seropositive or nonserotested hemophilic men, 280 couples reported pregnancies since January 1985, representing a fertility rate of 54.7 per 1000 women per year. This rate was comparable to the US fertility rate for this time period, suggesting that counseling was not as effective as had been hoped. 11,12 (The US fertility rate for 1985 was 66.2 per 1000 women aged 15 through 44 years old; for 1986, it was 65.4 per 1000; and for 1987 [provisional estimate], it was 66.1 per 1000.) Eight percent of these pregnancies were to women known to be HIV seropositive; 39% were to women not tested for HIV antibody. In part because of these findings, counseling and education of this population were intensified and federal monies were earmarked for transmission prevention within this population.18

In the fall of 1988 and in January 1989, we obtained follow-up information on

the HIV seropositive mother/father pairs and their offspring from the 1987 survey. We believed that this group could provide insight into three important perinatal HIV questions: (1) Why did reportedly intelligent and educated £t-risk couples procreate despite counseling and recommendations to the contrary? This information might be helpful in determining more appropriate techniques and content of counseling and education for various at-risk popu-Lations. (2) What were the family struc-Lures into which these children were born and how did parental HIV infection affect those structures? (3) Evidence exists that "cofactors" play a role n horizontal HIV transmission (eg., sexally transmitted diseases, immunodeficiency, drug usage, HIV sympcoms), 14,15 and some data suggest that naternal HIV symptoms are associated with infant symptoms of HIV. 16,17 Most studies of perinatal HIV transmission have as a primary postulate that cofacfor for horizontal transmission also play a role in vertical transmission (the National Institute on Drug Abuse Technical Review Meeting on Perinatal HIV Infection, October 17 and 18, 1988); however, to our knowledge, no data currently exist to support or refute this postulate. We therefore wished to also ask how the HIV infection status of children born to this survey's reportedly monogamous, well-nourished, nondrug-abusing, asymptomatic HIV-infected women compared with that reported for infants born to HIV-infected women in other risk groups.

PATIENTS AND METHODS

All HTCs reporting pregnancies of seropositive women in the 1987 survey were contacted by telephone in October 1988 and again in January 1989. Information was obtained on 23 of all 24 reported pregnancies, including 1 therapeutic abortion and 22 live

births, and also on three subsequent births to two of these seropositive women. One initially reported live birth could not be confirmed and one HTC required that one liveborn child (reportedly with acquired immunodeficiency syndrome [AIDS]) not be included herein, for reasons of confidentiality. The therapeutic abortion was to an HIV-asymptomatic woman and will not be discussed further. Information was provided from the medical records of the HTC and other physicians. No identified information was obtained and household members were not contacted for the purpose of this study. Human immunodeficiency virus serotesting in all cases was done locally and/or as part of ongoing research or health department studies using a screening assay, with confirmation with an appropriate second technique. Counseling concerning the meaning of antibody results, the risk of HIV transmission by sexual contact and from mother to fetus, and the mortality associated with HIV infection was reportedly given at least when results were shared with the tested individual, and often earlier. General HTC recommendations and individual counseling reportedly also included a recommendation against pregnancy for a sex partner of a hemophilic man; sometimes this recommendation was made in extremely strong terms. Of the women described herein, none were using illicit drugs or were known to have sexual relations other than those noted here; one hemophilic father used illicit drugs. (This low prevalence of other risk factors is consistent with questionnaire responses from the Centers for Disease Control's ongoing hemophilic household study¹⁸[Dale Lawrence, MD, unpublished data, 1989].)

A "planned pregnancy" was defined highly conservatively herein, as one in which one or both parents indicated to HTC personnel that he/she was actively attempting to procreate. Pregnancies that followed a parent's(s') indications of "readiness" for a child or conscious avoidance of pregnancy prevention were included herein as "unplanned." "Planned" thus indicates a very conscious choice on the parent's(s') part. The 95% confidence intervals (95% CI) were calculated for moderate or extreme proportions, where appropriate. 19

RESULTS Parental Characteristics

The fathers' ages ranged from 22 to 40 years, and mothers' ages ranged from 17 years to the mid-30s. Six (30%) of 20 couples were unmarried; for at least 5 of these couples, the couple was no longer together at the time of follow-up and the mother had the sole responsibility for their child. Three (21%) of 14 married

Planning of Pregnancy, by Knowledge of Parents' Serostatus: All Offspring of HIV-Seropositive Sex Partners of Hemophilic Men*

Couple Member	Prior to	Conception	Prior to Delivery		
Knowing Result	Planned	Unplanned	Planned -	Unplanned	
Neither	7	12	3	6	
Male/not female	1	0	1	0	
Female/not male	0	1	0	0	
Both	1	2	5	9	
Total No. of Pregnancies	9	15	9	15	

^{*}HIV indicates human immunodeficiency virus.

couples had since divorced, 2 of which had married because of pregnancy. Wives of two husbands who died of AIDS have new sexual partners. One remarried; her current spouse is reportedly using condoms for all intercourse. The other is pregnant by her current partner. Four couples (20%) were unemployed at the time of follow-up; five fathers (25%) and four mothers (20%) were employed in professional or technical areas; two fathers and one mother were employed in sales; and one father and three mothers were employed in office or security work. Seven mothers had no employment but full home care responsibilities; one mother was a high school student.

As of October 1988, 4 (20%) of 20 mothers had probable HIV-associated symptoms, 1 refused to return to the HTC after learning her antibody result, and 15 were known to be in good health. In seven fathers (35%) AIDS developed, and four of these died; four (20%) had HIV-related symptoms; two (10%) had severe liver disease; and seven (35%) were in good health. Only five couples were known to have consisted of two healthy partners.

Parental Serotesting and Notification

For 7 (29%) of the total 24 offspring, the father had been serotested prior to conception; two men were not informed of their test results until after the child was born—in one case due to a study investigator not notifying the HTC and in another, because the HTC could not locate the father. For 10 offspring (42%), the father was tested during the pregnancy (for 4, in the first trimester, for 4 in the second, and for 2 in the third); and for seven (29%), the father was tested after the birth. The mothers

knew the fathers' serostatus prior to the conception of four infants (17%), and their own, prior to the conception of five (21%). In nine pregnancies, the mother learned of the father's serostatus during the pregnancy; in four of these, the mother learned at less than 5 months' gestation. In seven pregnancies, the mother learned of her own serostatus during the pregnancy; in four of these, she learned at less than 5 months' gestation. Thus, for at least nine women, abortion would have been a medicolegal option in any state in the United States at the time she learned she was seropositive. Two mothers were serotested specifically because of pregnancy; one was tested because of possibly HIV-related symptoms in her infant. One was tested prior to her husband, when she was hospitalized for surgery; three were tested when AIDS developed in their hemophilic sex partners; four were tested by their health department or as participants in ongoing studies; and nine were tested in response to HTC recommendations (seven were tested within a month of their male partner's testing; one was tested 9 months following the man's testing; and one was tested at approximately 2 years after the man's testing).

Planned Pregnancies

Nine (37%) of these pregnancies were planned; three by at least the mother and six definitely by both parents (Table). One planned pregnancy was to a woman whose husband was tested prior to conception but who did not learn of his test results until after conception; this woman was tested during her pregnancy. Another planned pregnancy was in an unemployed woman whose unemployed boyfriend did not inform her of

his serostatus, although he knew it and had been fully counseled prior to conception; she was serotested after AIDS developed in the male partner, when the infant was 7 months old. Two planned pregnancies were to one couple told they were seropositive when the mother was in the first month of the second pregnancy: the mother also had a child from a previous marriage. Another planned pregnancy was to a Spanishspeaking couple with two other children; this couple was unaware that hemophilic patients were at risk of HIV infection. The wives of two hemophilic brothers living in different cities each had a planned pregnancy. Neither father had been counseled against procreation prior to the pregnancies; these fathers and mothers were all serotested during the pregnancies.

Reasons given for planning pregnancies, despite at least some HTC counseling in most cases, included denial that the offspring could really become infected ("It won't happen to us." "The risks are really low."); willingness to "take their chances"; unwillingness to consider the possible consequences ("I don't want to think about it"); a sense of invincibility, in that they had "conquered" hemophilia and would similarly triumph over HIV; and that "even if we are infected, we want a baby."

Unplanned Pregnancies

Two pregnancies were unplanned by a couple known to be seropositive prior to both conceptions but whose religion prohibited contraception. This couple's first child, also included in this survey. was the product of another unplanned pregnancy and was born 5 months before either parent knew his/her serostatus. This mother subsequently had a tubal ligation. Another unplanned pregnancy was to a couple of the same religion as the aforementioned couple. This couple also knew their serostatus prior to conception, already had a number of male offspring, and verbalized a desire for a girl. A fifth unplanned pregnancy of note was to an unemployed, unmarried couple having a long-term relationship. The couple did not know their serostatus prior to conception and the mother was of borderline normal intelligence. She had a subsequent pregnancy with the same sex partner that was terminated therapeutically; 2 months later she had a tubal ligation. The father was an illicit drug user and has no involvement in the care of this child. One pregnancy was to an unmarried couple expressing readiness for a child; the woman had reported consulting a family planning physician prior to conception and had been advised that being a sex partner of a hemophilic man did not place her at risk for HIV infection.

Pregnancy Outcomes

For these descriptions and analyses. we included only the 15 mother/father pairs and their 18 offspring with likely intrauterine HIV exposure, ie, those for whom the mother was either (1) seropositive on testing done prior to conception (n=5), during the pregnancy (first trimester [n=3], second trimester [n=23], third trimester [n=2]), at delivery (n=1), or within 1 month following delivery (n=2), or (2) tested more than 1 month after delivery, but had an offspring who was seropositive at older than 15 months of age (n=3, mother tested at 4, 7, and 16 months after delivery). These criteria excluded the following: one infant born 37 months prior to the mother's serotesting and breast-fed for more than 3 years (child was seronegative at 37 months of age and in good health at 58 months of age); one infant born 10 months prior to the mother's serotesting and breast-fed for 2 days (this child was seronegative at 19 months of age and in good health at 37 months of age); one infant born 5 months prior to the mother's serotesting, breast-fed for 12 months, and a sibling of two offspring included in these analvses, one of whom had symptoms of HIV infection (excluded child was seronegative at 3 months of age and in good health at 42 months of age); one infant born 24 months prior to the mother's serctesting and whose father died of AIDS 7 months after this child's birth (this child was seronegative at 31 months of age and in good health at 43 months of age); one infant born 6 months prior to his mother's serotesting (the mother would not return to the HTC after being told her test results; the mother's and infant's health and infant's serostatus are not known); and one infant born 5 months prior to the mother's serotesting and whose father died of AIDS 11 months after the child's birth (this child was seronegative at 11 months of age and in good health at 36 months of age).

None of the infants included in the descriptive analyses were born prematurely; median birth weight was 2.86 kg. (The US average birth weight for 1985 and 1986 was 3.37 kg.) Two infants were delivered by cesarean section, one reportedly because the mother was infected with HIV and herpes simplex virus type 2. These mothers were found to be seropositive in their fourth and sixth months of pregnancy; the infants were seronegative at 12 and 18 months of age. Two included infants were breast-fed, one for 9 to 12 months and one for 7 months, although the latter mother knew she was seropositive. The former mother was serotested when her child was 16 months old, because the child had marked cervical lymphadenopathy; the child was seropositive at 30 months of age. The second breast-feeding mother had also breast-fed an older infant, born 5 months prior to the mother's serotesting and not included in these analyses, for 12 months. Both her breastfed infants were seronegative, at 9 and 3 months of age, respectively, and they remain in good health. A third offspring of this same mother is included in these analyses and was not breast-fed (in response to intensive counseling of the mother by HTC personnel); this infant was seropositive and hospitalized at 4 months of age for presumptive Pneumocystis carinii pneumonia, responsive to appropriate antibiotic therapy, and at follow-up was failing to thrive. Offspring of two other mothers died of P carinii pneumonia confirmed by bronchial washings, one at 11 months of age and one at 4 months of age. By parental report and HTC provider observations, the remaining 15 (83%) of 18 children were in good health, without obvious developmental abnormalities, serious infections, failure to thrive, oral candidiasis, or diarrhea. One of these 15 children, who was seropositive at 44 months of age, had been diagnosed as having idiopathic thrombocytopenia in infancy; this has since resolved.

Serostatus and Clinical Status of All Infants

The median time since delivery of all 24 infants was 30.5 months (range, 8 to

57 months). Seven (30%) of 23 children were HIV seropositive at last testing. In addition, 1 child with presumptive Pcarinii pneumonia and failure to thrive was seropositive at 7 months of age and seronegative at the latest two testings. Four (31%) of 13 children serotested when they were older than 15 months of age were positive. Two of these four were also repeatedly HIV culture positive, and three seronegative children were also antigen negative; to the HTC personnel's knowledge, none had been tested for HIV-1 provinal DNA by polymerase chain reaction. Three infants (12.5%) were diagnosed as having Pcarinii pneumonia; two of these died of P carinii pneumonia and were seropositive at the time of death and one was the infant noted above, now seronegative, An additional two children seropositive when they were older than 15 months of age had questionably HIV-related symptoms (lymphadenopathy and idiopathic thrombocytopenia purpura). The mothers of these five symptomatic children were in good health at the time of follow-up. None of these children have any other known potential source of HIV infection besides maternal transmission. We estimated the minimum perinatal transmission rate for this group two ways. First, we included those followed up for at least 15 months and seronegative at latest testing, those seropositive when they were older than 15 months of age, and infants dying of P carinii pneumonia (AIDS) who would have been older than 15 months of age had they lived. One infant whose mother was tested because of his symptoms and one infant without serotesting were excluded. The minimum transmission rate was 25.0% (5/20) (95% CI, 9.6% to 49.4%). (Median birth weight of these five infants was 2.9 kg [range, 2.7 to 3.5 kg].) Second, in addition we excluded any child whose mother was serotested more than 1 month following the child's birth, giving a minimum transmission rate of 23.1% (3/13) (95% CI, 6.2 to 54.0).

Sibships

Three of three sibships included one pregnancy and one seropositive child, although not all seropositive children were older than 15 months of age when last tested and cannot therefore be con-

sidered necessarily infected: one pair had an older sibling seropositive at 26 months of age and a younger sibling seronegative at 17 months of age; a second set had the oldest sibling (not included in the analyses) seronegative at 3 months of age, the second sibling seronegative at 9 months of age, and the youngest sibling seropositive at 4 months of age and subsequently seronegative but symptomatic with presumptive P carinii pneumonia and failure to thrive; and a third pair had an older sibling seronegative at 11 months of age and a younger sibling seropositive at 7 months of age.

COMMENT

To our knowledge, this is the first study to examine reasons why couples with stable health care provider contacts would fail to implement public health guidelines for prevention of HIV transmission. In 1987, we had hoped to find the fertility rate for this population nearly zero, and certainly not comparable to that of the United States as a whole, since widely disseminated Public Health Service and NHF recommendations at the time of these pregnancies were for at least HIV-untested or seropositive hemophilic men to avoid unprotected intercourse and procreation until more was known about HIV transmission and outcome risks.1-10 We thus wished to find out more about whether seropositive couples were aware of the male and/or female partners' serostatus at the time of the pregnancies, if the mothers were serotested because of pregnancy or a desire for pregnancy. whether therapeutic termination of pregnancy would have been a medicolegally available option at the point parents were serotested, whether the pregnancies were planned, couples' attitudes about the fetuses'/infants' risks of HIV infection, and the effects of HIV on the family structure into which these children were born.

Thirty-seven and five-tenths percent of the pregnancies (nine) were actively planned; in at least 37.5% (nine) of all pregnancies the mother learned of her seropositivity at a point in which pregnancy termination would have been a medicolegal option. These data support the following impediments to recom-

mendation compliance: lack of information, a strong level of denial (including a sense of invincibility because they had already dealt successfully with the potential problems associated with hemophilia), religious beliefs, and poor communication at all levels, including among research coordinators, HTC personnel, hemophilic men, and these patients' female sex partners. Finances are now in place to help HTCs address these problems. ¹³

It would be interesting to compare the characteristics of these childbearing HIV-infected couples with those of nonprocreating HIV-infected hemophilic men and their sex partners. Unfortunately, to our knowledge, data are not available concerning the demographic characteristics, occupations, marital status, and marital stability of the HIVseropositive or the general US hemophilic population. The age distribution of the couples discussed in this article was certainly neither lower than that of a cohort of factor-product recipients from across the United States for which participation was limited to persons older than 13 years of age (median age, 22 years: n = 220) nor lower than that of hemophilic patients receiving care at California HTCs^{20,21} (11% were 5 years old or younger; 15% were 6 to 12 years old; 7% were 13 to 16 years old; 9% were 17 to 20 years old; and 58% were 21 years old or older; n = 1438).

A recent study suggested that counseling and education can lead to increased condom usage by HIV-infected African prostitutes because of concern about infecting their clients.22 There is every reason to expect that with counseling and education, hemophilic men will show a similar concern for their wives, girlfriends, and potential offspring. However, our data support a need for outreach to ethnic minorities and women having relatively unstable relationships with hemophilic men, all of whom might not know HTC personnel well or consider these personnel their own health care providers. Also, it may be useful in counseling hemophilic couples considering parenthood to note that the offspring of these particular couples were faced with a high rate of parental morbidity/mortality (one or both parents were clinically symptomatic in 14 [74%] of 19 households) and

conjugal instability (50% of households were not intact).

This study also provides case-specific information pertinent to a number of perinatal HIV debates: the roles of vaginal delivery and breast-feeding in HIV transmission, the relation between pregnancy and maternal symptoms, the relation between maternal symptoms and infant symptoms, and the effect of HIV on intrauterine growth and length of gestation. We will briefly review our data in relation to several of these. Human immunodeficiency virus has been isolated from breast milk; breast milk was implicated as a possible source of HIV infection for at least four infants23-26 and epidemiologically it was linked to higher rates of infant seropositivity.27 The Public Health Service recommends that HIV-seropositive women not breast-feed.2 In our study, five children were breast-fed, two by mothers who were known to be seropositive while breast-feeding. Four were healthy and seronegative at follow-up. and one breast-fed infant was seropositive at 30 months of age. It has been suggested that HIV symptoms in mothers is associated with symptoms in infants; however, subsequent evaluations in one of these studies failed to support the initial finding. 16,17,28 All our study mothers were healthy at the time of pregnancy and the mothers of the five symptomatic children were in good health at follow-up. Conversely, the four mothers who were symptomatic at follow-up had healthy, seronegative children. Finally, the infants in our study were born full term, with birth weights close to the US average, suggesting that maternal HIV infection does not necessarily lead to clinically significant intrauterine growth retardation or prematurity, findings consistent with those of three large, multicenter studies involving mothers in other risk groups. 27-29

To our knowledge, this is the first study to examine the rate of vertical HIV transmission and maternal/child symptoms in women who had few or no purported "transmission cofactors", eg, promiscuity and associated sexually transmitted diseases, intravenous drug abuse, malnutrition, and HIV symptoms. Indeed, few data exist to quantitate the risk of vertical transmission by

HIV-infected women in any risk group. Most studies are based on symptomatic infants, siblings, or mothers, and thus these results cannot be generalized. 80,51 Four studies have been published in which seropositive women were followed up to completion of pregnancy. In one report, 92 completed pregnancies of drug-abusing women were evaluated: 56% of the women were reportedly HIV seropositive, but the timing of antibody testing in relation to the pregnancy was not given.30 Seventeen children had AIDS or AIDS-related complex develop; the latter was not defined and the length of evaluation was not stated. The rate of transmission was estimated to be approximately 35%. In another prospective, multicenter study of seropositive women serotested prior to or at delivery, 100 infants were followed up for more than 15 months.2 Eighty-five percent of the enrolled women had abused drugs: 7% had contact with an infected drug-abusing sex partner as their only certain HIV risk factor. Fifteen children remained seropositive and an additional four died of AIDS, giving a minimum transmission rate of 19%, based on serologic findings and symptoms. An additional five were virus or antigen positive, giving a final rate of 24% (95% CI, 16% to 32%). However, not all children, and not a representative sample, had cultures taken or were antigen tested. The third study, also a multicenter one, estimated a transmission rate of 32.6%, based on serologic findings and symptoms for 89 children older than 15 months of age (95% CI, 22.3% to 42.9%, by our calculations).29 The fourth study was of 308 motherchild pairs in 51 obstetrical and pediatric centers in France; 62% of the mothers were drug addicts. Thirty-two (27%) of 128 infants had serologic "or other" evidence of HIV infection at 18 months of age. 27

Additional smaller or less advanced studies include prospective studies of seropositive women from Haiti, Zambia, and Kenya and of additional groups of seropositive drug-abusing women or female sex partners of drug-abusing men²² (information from the National Institute on Drug Abuse Technical Review Meeting on Perinatal HIV Infection, October 17 and 18, 1988). In all of these reports, transmission rates

ranged from 10% to 41%, based on data from seroevaluation at older than 12 months or older than 15 months of age: transmission rates were often based on culture and antigen assays, as well as serotesting. Thus, these transmission rates are consistent with our own mininum rate of 25.0%, despite the differences in transmission categories/lifestyles and the absence of symptoms in cur seropositive mothers. Furthermore, evidence is accumulating that infected children, unlike infected adults, may not infrequently be seronegative. 16,27,33-85 Therefore, we cannot overemphasize that our rate, based solely on clinical symptoms or positive serologic findings at older than 15 months of age. represents a minimum transmission risk. We conclude that infants of HIVinfected women are at extremely high risk of HIV infection, even if the intected mother is healthy and has no purported cofactors for vertical HIV transmission.

The Hemophilia-AIDS Study Group collaborating on this project includes the following: Roxme Anderson, RN, MSN, PNA, Children's Hospital Medical Center, Cincinnati, Ohio; Jeannine Aquino, MPS, Cornell University Medical Center, Hew York, NY; Ginny Cosgrove, Children's Hospital of Michigan, Detroit; Robin Dretler, MD, De-Zalb General Hospital, Atlanta, Ga; Marilyn L. Tord, EdD, Co-Director, Mountain States Hemo-►hilia Center, University of Utah, Salt Lake City; Ann Forsburg, MA, Research Associate, Worceswer (Mass) Memorial Hospital; Alice Forster, RN Mount Sinai Hemophilia Center, New York; W. Zeith Hoots, MD, Gulf States Hemophilia Center, Bouston, Tex; Ann Hunter, MSW, The National ∃emophilia Foundation Georgia Chapter, Atlanta; Busan Karp, RN, MS, University of California, San Prancisco; C. Thomas Kisker, MD, Hemophilia Project Director, University of Iowa Hospitals and Clinics, Iowa City; Emigh Litch, RN, Children's ∃ospital of Michigan, Detroit; Kathy Mendez, RN, MSN, Mary Ann Miller, University of Cincinnati Ohio) Medical Center; Marilyn Obedzinski, RN, Zan Francisco General Hospital; Bernadette Sqroi, RN, Thomas Jefferson University Hospital, Philadelphia, Pa; Beverly Stevens, RN, Oklahoma Chil--Iren's Memorial Hospital, Oklahoma City; Betty Stocks, RN, Maine Hemophilia Treatment Center, Portland; Margaret Weintrub, MD, University of California, San Francisco; Arnette Wolfer, RN, Allentown (Pa) Hospital Hemophilia Treatment Center; and Karen Wulff, RN, Louisiana Compreiensive Hemophilia Care Center, New Orleans.

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CORRECTION

Incorrect Spelling of Author's Name.—In the article entitled "Wood-Burning Stoves and Lower Respiratory Tract Infection in American Indian Children," published in the January issue of AJDC (1990;144:105-108), the second author's last name was spelled incorrectly. It should have read Morgenlander (not Morganlander, as submitted by the authors).

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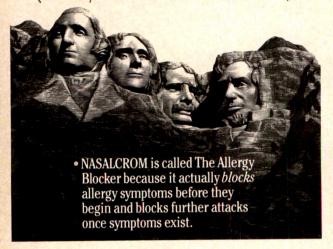
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Special Contribution

P Values

George W. Brown, MD

The use of P values (eg, $P \le .05$ or similar notation) is commonplace in research reports in medical journals. There are two kinds of P values of interest to journal readers. One is the value selected by the researcher as the accepted "risk of the type I error." "a risk," or "rejection region." It is a widespread custom to use .05 as a convenient cut-point for "statistical significance." (This convention is a part of the statistical legacy of the British statistician, Sir Ronald A. Fisher.) The second kind of P value is the observed value from a statistical test, that is, the value resulting from application of a test (eg, t or χ^2 test) to observations. Since the "P" in P value implies a probability, most medical journals use an uppercase P, reserving a lowercase p to signify proportions. The aim here is to look at some slippery features of P values that are not often discussed in medical journals.

The observed P value is meaningful only when the state of nature (unknown to the data analyst) is that the hypothesis of no difference (null) is true and should not be rejected. When a statistical test, such as the t or the χ^2 test, is used to evaluate "significance," the meaning of the resulting P value may be misunderstood. It does not mean that the decimal following the P is the probability that the hypothesis of "no difference" is correct. The P value is the probability of observing a result as extreme as or more extreme than the one in hand, if the result is entirely due to chance (and the null hypothesis should not be rejected). If the P value is quite small, the analyst may reason that some alternative to the null hypothesis might better explain the observations.

The idea of the type I error (α level) is straightforward when the focus is on only one application of a statistical test. The type I error is analogous to the "false-positive" test in diagnosis. It is the risk of concluding that an important difference exists, when chance alone is operating. The type II error of statistical testing is similar to the "false-negative" diagnostic test: something important is present, but it is missed.

There is sometimes great pressure in biomedical research to repeat statistical tests on different kinds of observations on the same subjects or test objects. However, when more than one trip is made to the statistical well, mathematical complications occur that change the interpretation of the P value. Such repeated "calls on chance" inflate the probability that one or more small P values will be found, purely by chance, among the several that are examined.

The researcher may rationalize the use of repeated statistical tests by logic something like this: "A P value of .05 means that 1 test in 20, with no real difference present, will be judged 'significant.' So, in 19 of every 20 statistical tests, my conclusions will be valid." Well, almost; but not exactly.

Over many repetitions of clusters of 20 statistical tests, at $P \leq .05$ for each. the analyst would encounter on the average 1 in 20 that signaled "significant," although only chance is operating. This expectation applies to the average rate of occurrence of $P \leq .05$, but it oversimplifies the vagaries of chance that occur when clusters of tests are done.

Suppose two groups of infants are being compared in a clinical investigation. The two groups of infants are not substantially different in biological features, such as birth weight, body length, head circumference, hematocrit, and so on. A t test is used to compare the birth weights of the two groups of infants; the P value is set by the analyst at $P \leq .05$. The random variation in birth weights among the infants would suggest wrongly, in about 1 comparison in 20, that an important difference between the two groups in average weight was present.

Some familiar mind games provide a feel for a probability of .05. Suppose we repeatedly toss a cohort of four honest coins, all four will land as "heads" in about 6.25% of the group tosses. Four "tails" will occur in about the same proportion. When the coins are tossed in sets of five coins at a time, five "heads" occur in about 3% of the group tosses.

What does this have to do with biology? If gender were truly random, half male and half female, we would expect about 6.25% of four-child sibships to be all boys; another 6.25% would be all girls. The chance of all four children being the same (but unspecified) sex would be 12.5%.

Returning to the two groups of infants proposed above, suppose a second t test is done, this time on head circumference. If this second test is done at $P \leq .05$, the chances of getting a statistically significant test on either the first (birth weight) or the second (head circumference), or both, is .0975. (The chance of "significant" on the first test is .95. The chance on both the first and second is .95 × .95. The chance of "significant" on either the first or second or both is $1 - .95^2 = .0975$.) Remember, the two sets of infants do not differ in any important ways, other than by random variation.

A third statistical test is done, perhaps on length. The probability of one or more "significant" tests has grown to .1426, that is, $1-.95^{\circ}$. In a cluster of three tests, none, 1, 2, or all 3 may be "significant." When three tests are done at once, the a level inflates to about 1 in 7, rather than 1 in 20.

If the analyst is unaware of this ballooning of the a risk, he/she may go on to test fourth and fifth variables, say bilirubin and cholesterol values. The probability of at least one test showing $P \leq .05$ has now inflated to .2262, or about one in four. The probability that exactly one of the five tests will have $P \le .05$ is .2036; the probability that any two of the five will be "significant" is

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.0214. Since the two groups of infants are not really different, we would wish that all five of the tests be "not significant", but the probability of finding all five tests not significant has shrunk to .7738, that is, 1-.2262.

This argument can be extended to however many repeated statistical tests might be done on the two groups. The Table shows that with 10 repetitions, the probability of 1 or more being judged significant is about 40%. There is a 7.5% chance that 2 of the 10 will be judged significant.

If researchers were imaginative enough to perform, say, 30 statistical comparisons on the two sets of subjects, the probability of finding one or more significant test is up to .7854. There is almost a 5% chance of finding four with $P \le .05$ among the 30 comparisons.

BINOMIAL EXPANSION

Suppose a very large surgical residency program at Mekka Medical Center consistently had 20% women and 80% men. It was the custom of the chief of surgery to select at random three residents each year to be his special preceptees. This eminent teacher was accused of being prejudiced against women, because he had not chosen a set of three women in living memory. How would the counts of the randomly selected men and women residents be distributed over the years?

There is a venerable and useful theorem, usually first encountered (then promptly forgotten) in high school algebra, that predicts the long-range expectations in matters of this sort. The binomial theorem deals with situations in which elements or events occur in just two forms (binomial means "two names"), such as ill/well, success/failure, or men/women.

In the present example, the theorem

 $(.20 + .80)^3 = (.20)^3 + 3(.20)^2(.80) + 3(.20)$ $(.80)^2 + (.80)^3$ which is an algebraic way of saying:

Three women = $(.20)^{\$} = .008$ Two women, one man = .096 One woman, two men = .384 Three men = $(.80)^{\$} = .512$ Total = 1.000

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In less than 1% of the group selections would there be all women, even when done honestly and objectively.

Proportion of 0, 1, 2, 3, 4, 5 . . . n 'Significant' Results With Clusters of Tests of Size 10, 15, 20, or 30*

	No. in Cluster of Tests Done				
No. of Tests With Outcome, P≤.05	10	15	20	30	
0	.60	.46	.36	.21	
1	.32	.37	.38	.34	
2	.07	.13	.19	.26	
3	.01	.03	.06	.13	
4		.005	.01	.05	
5				.01	
n	9.8×10 ⁻¹⁴	3.1×10 ⁻²⁰	9.5×10 ⁻²⁷	9.3×10-40	

*The decimals in the body of the Table are the probabilities of observing a P value of ≤.05 the number of times shown on the left. It is assumed that the same samples are being compared in regard to "n" variables, eg, height, weight, bilirubin value, etc. It is also assumed that the different groups of subjects do not differ except in regard to random variation.

A less artificial example is seen in clinical genetics. Consider a large number of couples, where both are carriers of an autosomal recessive gene. Among a large number of their offspring, one fourth will be affected by the condition and three fourths unaffected (although some will be carriers). Among those families that have four children, what proportion would have all four unaffected?

 $(.25 + .75)^4 = (.25)^4 \dots (.75)^4 = (.0039) \dots (.3164)$

Among all the sibships of four, 31.6% would have all four free of the disease. In 69.4%, at least one child would be affected. In the worst case, in about 4/1000 (.0039) such sibships, if no measures were taken to limit offspring, all four would be affected. To those who are comfortable with such algebra, this is banality to the fourth power; to others, the response may be, "So what?" So, how might the binomial theorem be instructive in understanding the pitfalls of repeating statistical tests, each performed with the risk of the type I error (α) set at $P \le .05$?

If one were habitually to do statistical tests at $P \le .05$, in aggregates of 20 tests, the occurrence of "significant" P values would range from 0 to 20. The Table shows the proportion of 0, 1, 2,...n "significant" results with clusters of tests of size 10, 15, 20, or 30.

It is apparent that most statistical tests will be "not significant" when there is not a real difference between groups. However, there will be some "significant" *P* values observed, and some decision will have to be made

about these outcomes. The analyst has no guidance as to when a "significant" test is valid or is merely one of the expected low P values due to chance. The very small probability shown in the Table at n=20 is the chance of $all\ 20$ tests showing $P \le .05$ when each independent test is evaluated at an α level of .05.

The numbers in the Table are found by expanding a binomial of this type: $(p+q)^n$, where p=.95, q=.05, and n is the number in the cluster of tests being done. The details of the algebra can be found in any algebra book or statistics text. The main message is that the investigator may accept an average risk of 1 in 20, but scattered around that average will be more "significant" test results than the average of 1 in 20 implies.

MULTIVARIATE STATISTICAL ANALYSES

Many biostatisticians consider this preoccupation with P values as archaic and simplistic, in view of modern multivariate methods of analysis. There are several methods, usually requiring computer processing, that permit simultaneous evaluation of sets of "predictor variables," such as birth weight, age, sex, socioeconomic status, etc, in relation to one or more "outcome variables." Although these elegant analyses are seen with some frequency in the biomedical research literature, we will probably always have simpler clinical trials that employ traditional P values when the results are evaluated.

The multivariate methods also adjust for another technical problem related to statistical tests done on several differ-

ent variables observed in the same subjects. Different clinical variables are often highly correlated with each other. The hemoglobin level is strongly associated with the hematocrit and red blood cell count; weight is correlated with height. The complication occurs when one such variable, by chance, appears to be different in one group of subjects as compared with another. A second variable, if highly associated with the first, may also appear to be "significantly different." Instead of drawing only one wrong inference, the analyst may be further misled by the correlation among variables, perhaps leading to several wrong conclusions.

Statistical authorities urge that we be clear about the source of the error, when a faulty conclusion is drawn from an observed P value. The error is not in the P value itself; it is mathematically and logically correct. The error is in the (quite reasonable) inference drawn: "Since this P value is so small, some alternate to the null hypothesis must be entertained."

A DISSENTING VOICE

There may be some risk of exaggerating the impact of inflation of the type I error when repeated statistical tests are performed. O'Brien² suggests that α inflation is best dealt with by a judicious application of statistical tests by the data analyst. If the analyst is conservative and restrained in the questions asked of the research data, the impact of α inflation may be minimized. In short, the analyst should not perform a statistical test on everything in sight (and journal editors should not insist on repeated P values when research reports are submitted for publication).

O'Brien² offers a fascinating conundrum related to P values. Suppose a clinical investigator at MegaClinic conducts a clinical trial on treatments A, B, and C in three groups of patients. At the conclusion of the trial, the data analyst might perform three comparisons: A vs B, A vs C, and B vs C. The well-trained analyst would see that the P value for each comparison should be adjusted downward from the overall $P \le .05$. That is, he/she would penalize himself/herself for doing three statistical tests.

Now suppose that out in Podunk a study was conducted of just A vs B.

Another investigator in Boondock studied A vs C. A third researcher in Foozball studied B vs C. They each used, quite appropriately, $P \le .05$ for evaluating their two-sample results.

The question posed by O'Brien² is disconcerting: Why should the investigator who has the most comprehensive overview of treatments A, B, and C be punished with an adjustment to the P value that is not imposed on the separate studies done in three less elaborate trials? In short, the most comprehensive study is penalized for being just that. We should leave the resolution of this enigma to the experts in probability.

MULTIPLE PEEKS, AS RESULTS ACCUMULATE

Researchers often have an irresistible urge to look at the results, while the project is in progress. The researchers may be driven by scientific curiosity or by a dwindling budget to examine the accumulating data before the planned sample sizes have been reached, with the aim of stopping the study as soon as the results "look good." Unfortunately, there is a statistical penalty that must be assessed for each interim peek. If the investigator planned to evaluate the completed clinical trial by using $P \leq .05$, a peek halfway through the study would require that the P value at that peek be, say, .03, before "significance" could be inferred.

The need to evaluate results as they accumulate may not be based on the avid curiosity of the investigator. There is an ethical obligation to terminate the investigation as early as possible, so that no participants are unnecessarily subjected to an inferior intervention; also, the inescapable risks that occur in clinical trials should be kept to a minimum. A recent investigation of the benefits of cryotherapy for retinopathy of prematurity was terminated earlier than originally planned when the accumulating data indicated convincingly that one intervention was clearly superior.3

The matter of multiple peeks at accumulating data is not often discussed in the clinical literature, probably because there is some disagreement among statisticians about how to deal with the statistically complex issues. A convenient

table for adjusting *P* values for repeated peeks can be found in a brief report by McPherson.⁴ The issue of "stopping rules" based on looking at accumulating data has been studied in depth, but the technicalities are rather overwhelming for the nonstatistician.⁵⁸

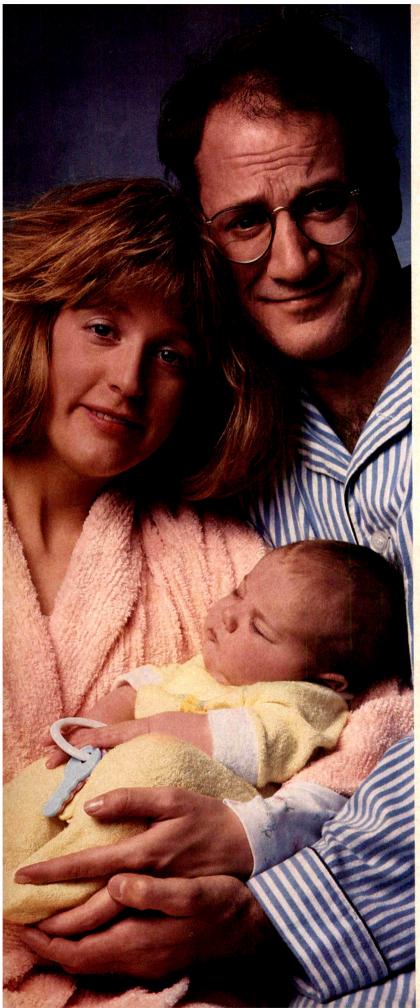
The best course of action is to avoid peeking at the results of the clinical trial while it is in progress. If there are major ethical issues involved, it will be necessary to consult with a statistician who knows about multiple peeks and stopping rules. Silverman (CPL) comments: "Bettors who declare that the race is over when their horse is ahead have trouble collecting their money."

COMMENT

Repeated statistical tests on the same elements or subjects introduce a complication called "a inflation" or "increase in the risk of the type I error." Statistical textbooks suggest that this inflation can be adjusted by dividing the desired a level, say $P \leq .05$, by the number of repeated statistical tests done. If four statistical tests are done on the same two groups of subjects (say on bilirubin, creatinine, serum urea nitrogen, and blood glucose values), then each test would be evaluated at .0125, rather than at .05. This is called the Bonferroni adjustment. For large clusters of statistical tests, it may not be appropriate. Perhaps the best practice is to be extremely selective in deciding which variables should be evaluated by statistical tests.

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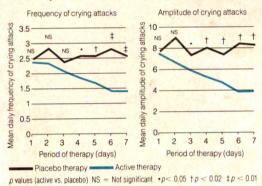
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Educational Interventions

Hugh D. Allen, MD, Columbus Ohio Fredric Burg, MD, Philadelphia, Pa Harold Levine, MPA, Galveston, Tex Barbara Starfield, MD, Baltimore, Md Larrie W. Greenberg, MD, Washington, DC

Purpose.—This department is intended to share information concerning educational efforts in the broad field of pediatrics. We welcome studies on the following topics: undergraduate and graduate education in medicine and allied health occupations; continuing education of health professionals; education of patients and families; and health education for the general public, the community, and organizations that contribute to the promotion and improvement of the health of children.

Editorial Comment.—Pediatrics as a career choice has been considered satisfying and dissatisfying. What are the career counseling characteristics (if any) of your program? How do they compare with those encountered with this survey of 155 programs? By the way, what and how are your trainees doing? This interesting article may lend some insight.—H.D.A.

Career Counseling Practices in Pediatric Residency Training Programs

Larrie W. Greenberg, MD; Leslie S. Jewett, EdD; Arnold H. Einhorn, MD; Zandy B. Leibowitz, PhD; Lawrence F. Cohen, MD

• Although there has been an emphasis on career satisfaction in pediatrics and on motivators that impact on resident career selection, little attention has been directed toward the career development process in pediatric residency training. This report summarizes the results of a survey conducted of 155 pediatric residency program directors about their counseling practices. Implications of the results and recommendations are discussed to improve this process.

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Choosing a career is one of the most difficult decisions a resident must make during his or her training. This

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This report was presented in part at the Ambulatory Pediatric Association Meeting, Anaheim, Calif, April 30, 1987.

Reprint requests to the Office of Medical Education, CNMC, 111 Michigan Ave NW, Washington, DC 20010 (Dr Greenberg). decision is critical for young physicians in achieving their career goals and important to the success of their life plans.

In the 1980s, making a career choice became even more complex and stressful for residents. Many changes are taking place in the health care environment that impact on career opportunities. Changing practice styles, the emergence of managed care systems, the projected oversupply of physicians, more vigilant utilization of services and reimbursement, and the change in the nature of patients' problems are only some of the new issues residents must address in selecting a career.^{1,2}

Pediatrics, like other specialties, has experienced significant changes in practice and academic medicine. Improved technology and scientific advances have increased specialization and resulted in new demands on pediatricians, often in areas in which they have received minimal training.³

In the past, some pediatricians expressed dissatisfaction with their career choices. The American Academy of Pediatrics' survey in the mid-1970s found that almost all (96%) of the re-

sponding pediatricians would become physicians if given the opportunity to do it over again; however, only 84% would choose pediatrics. Practitioners (18%) were more likely than academicians (9%) to be dissatisfied with pediatrics as a career choice.4 Another study found career dissatisfaction and burnout syndromes in pediatricians who provide primary care in outpatient settings, work in hospitals with severely ill and dying children, or work in academia and must balance the demands of the university with the pressures of patient care.5 A more recent study by the American Academy of Pediatrics⁶ revealed that only 5% of respondents were dissatisfied or very dissatisfied with their careers, but 18% anticipated making a career change in the next 5 years. In fact, pediatricians have opted for other fields, such as radiology or dermatology, or have taken administrative positions. Underlying this shift is a presumed dissatisfaction with pediatrics, although the motivation is unquestionably multifactorial.

Research on the career development process has focused primarily on how

Table 1.—Follow-up Process				
Follow-up Method	No. (%) of Responding Programs*			
No follow-up	69 (45)			
Follow-up	86 (55)			
Alumni newsletter	16 (19)			
Correspondence/telephone	12 (14)			
Informal	25 (29)			
Personal contact	32 (37)			
Questionnaire	7 (8)			
Reunions at hospital				
or national meetings	55 (64)			
Miscellaneous	11 (13)			

*Percentages total more than 100% because respondents used more than one type of follow-up.

medical students choose a career.7-9 However, this process does not abruptly end on graduation from medical school. A physician's career is composed of different stages where achievements should fit into realizing career and life goals. A critical decision point for physicians in determining the next career stage occurs during residency. Residents are faced with significant career choices within their specialty, such as traditional fee-for-service practice, a health maintenance organization, academics, research, administration, and the military. Yet, it appears that career counseling for residents has received variable emphasis.

In response to the dissatisfaction of some pediatricians with their career choices and the lack of information on the career development process during the residency program, the Office of Medical Education at Children's National Medical Center, Washington, DC, conducted a survey of pediatric residency training program directors (RTPDs) in the United States. The purpose of this survey was to determine the strengths and weaknesses in the career counseling of pediatric residents and ways in which career planning with residents could be improved to increase their satisfaction with career choices. This report summarizes the survey.

METHODS

The authors sent a questionnaire in November 1984 to RTPDs listed in the 1984-1985 Directory of Graduate Medical Education Programs. The questionnaire was sent again in February 1985 to RTPDs who had not responded.

		Table 2.	-Time Spe	ent in Cou	nseling*		
							(%) of ondents
Resident		No. of Hours		No	0-2 h Per		
Year Mean	SD	Median	Mode	Range	Time Year		
Pl-1 (n=139)	4.50	6.16	3.0	2.0	0-55	21 (15)	66 (48)
PL-2 (n=139)	5.83	5.89	4.0	2.0	0-30	9 (7)	48 (35)
PL-3 (n=137)	8.10	8.15	5.0	4.0	0-50	4 (3)	23 (17)

*Analysis of variance (ANOVA) (postgraduate level 1 (Pl-1) vs postgraduate level 2 (PL-2) vs postgraduate level 3 (PL-3) – F = 9.88; P = .0001. The results of pairwise \pm tests with Bonferroni correction were as follows: Pl-1 vs PL-2, not significant; Pl-1 vs PL-3, P = .001; and PL-2 vs PL-3, P = .05.

The survey questionnaire asked respondents for the career choices and follow-up of residents graduating from their programs and a description of their program's career development process with residents, including the following: (1) the amount of time spent with residents in career selection, (2) the adequacy of counseling time, (3) the top five priorities in career counseling, (4) the major limitations in the career counseling process, and (5) recommendations for improving career counseling for residents.

Statistical analyses on the time spent in career counseling were performed using the analysis of variance (ANOVA) and pairwise tests with a Bonferroni correction.

RESULTS Respondents' Demography

One hundred fifty-five of those surveyed (61%) returned completed questionnaires after two mailings. Of these, 72% (112) were RTPDs, 28% (43) were departmental chairpersons, and 79% (122) were full-time faculty. Of the 21% on the part-time faculty, 97% spend at least one half their time in the residency training program. The mean time respondents held their present position was 6 years.

Career Choices

Respondents reported that most residents (68.2%) who had completed their training within the past 5 years chose careers in practice. Twenty-three percent selected academic medicine and 7% opted for subspecialties, such as child psychiatry, dermatology, and pediatric anesthesiology/intensive care.

Follow-up

Thirty-seven percent (57) of the programs have no formal follow-up of their trainees after the completion of training. These data are summarized in Table 1.

Frequency of Counseling

When asked how often they actually counseled residents regarding their career choices, the majority of respondents did not specify the frequency at any of the three training levels. In those programs where the process appears more defined, residents meet semiannually to monthly for counseling, although the number of sessions per year does not change during the 3 years.

The content of the counseling sessions was often not specified, although the counselors focused on future options for residents more frequently as they progressed from their postgraduate level 1 (PL-1) to postgraduate level 3 (PL-3) years. Fewer than 10% of the respondents reported that they addressed residents' personal concerns and elective choices.

Two thirds of the responding programs use faculty advisors (40%), the chairperson (11%), and the RTPD (15%) as counselors, although one third of the respondents did not specify any group. Departmental chairpersons assumed more responsibility for counseling PL-3s (15%) than PL-1s (8%) and PL-2s (10%). The involvement of the RTPD remained constant for the 3 years of training. One respondent reported using a professional career counselor for its residents.

Some training programs (3% to 14%) reported including 1-hour group meetings regarding career options or a more in-depth experience using seminars or retreats.

Time Spent in Counseling

Table 2 outlines the amount of time devoted to residents in discussing career options. Of interest is that at the PL-1, PL-2, and PL-3 levels, 15%, 7%,

Table 3To	p Five	Priorities in
Co	unseli	ng

Counselling				
Priority	No. (%) of Respondents*			
Knowledge in general information and options regarding career choices Assessment of the resident's strengths, weaknesses, motivation, competence, and	90 (58)			
personality Familiarity with the	66 (43)			
job market Matching the trainee	60 (39)			
to a career Life-style and family	50 (32)			
concerns	40 (26)			

^{*}Percentages total more than 100%.

and 3%, respectively, of programs offer no formal counseling at all. The mean number of hours devoted to counseling increased with each training level (P = .0001).

Forty-seven percent (n=73) of respondents reported that too little time is spent in career counseling, 52% (n=81) perceived the current amount of time as appropriate, and 1% (n=2) stated there is too much emphasis on counseling.

Top Five Priorities of Counseling

Table 3 outlines respondents' top five priorities in the career counseling of residents.

Major Limitations in Counseling (Table 4)

Time constraints of an already overextended faculty and the subjectiveness of the process were reported to be the major limitations by almost one half (43%) of the respondents. There were no statistically significant correlations between any of the listed major limitations in counseling and the number of years that respondents held their present position. In examining the experience of the RTPD or chairperson and how it correlates with the perceived rating of the counseling program, there was a poor correlation ($r_s = -.1466$), but as the experience of these faculty members increased the program was rated more highly.

Evaluation of Counseling

Respondents were asked how they thought their trainees would evaluate

Table 4.—Major Limitations in Counseling

THE RESERVE OF THE PARTY OF THE			
Limitation	No. (%) of Respondents*		
Time	67 (43)		
Subjectiveness	67 (43)		
Lack of knowledge of			
what residents			
want to know	52 (34)		
Lack of background			
in counseling	41 (26)		
Large number of			
residents to be			
counseled	32 (21)		
Counselor bias	26 (17)		

^{*}Percentages total more than 100% because respondents provided more than one limitation.

the quality of the counseling in their programs. Only 22% of the respondents thought their programs were perceived by residents as "above average" to "outstanding" in their career counseling. Forty percent of the programs were reported to be considered "average."

Program respondents who reported that their career counseling was perceived to be "outstanding" or "above average" were more likely to state they did an appropriate amount of counseling compared with those who did too little counseling (P=.0027). Programs rated as above average or outstanding were less likely to have counselors with time limitations (P=.007) or counselors who felt they lacked counseling skills (P=.023).

Ways to Improve Counseling

Seventy-six percent of the respondents reported that the career counseling of their residents should be improved. Suggestions to improve counseling included appropriating sufficient time, developing a formal counseling system, and knowing the market-place (Table 5).

COMMENT

Research in career counseling has focused almost exclusively on the process by which medical students select a specialty. However, in a recent study focusing on pediatric career choices, Adler et al¹⁰ reported that there has been poor documentation in the literature on how training impacts on career choice. Their study examined residents' per-

Table 5.—Suggestions to Improve Counseling (n = 97)

Suggestion		(%) of ndents*
Appropriating		
sufficient time	20	(21)
Developing a formal		
counseling		
system	18	(19)
Knowing the		
marketplace	13	(13)
Seminars/		
workshops/		
audiovisual aids	9	(9)
Improving		
counseling		
process	8	(8)
Increasing exposure		
to primary care	8	(8)
Counseling earlier in		
training	8	(8)
Miscellaneous (eg,		10 10 5 6
more resident-		
initiated, research,		
availability of		
counselors)	18	(19)

^{*}Percentages total more than 100% because respondents provided more than one suggestion.

sonal attributes and training program characteristics that may have influenced the final career decision. Benson et al¹¹ identified characteristics of residents that are associated with intentions to pursue an academic vs full-time private practice career. In contrast, our survey examined the actual career development process as conducted in pediatric residency training programs throughout the country.

Recent trends have confirmed that the majority of pediatric residents continue to select practice as their career choice. The Association of American Medical Colleges' survey of the 1985 medical school graduates revealed that 67% of pediatric residents were planning to enter general pediatrics, with 25.8% considering subspecialties. 12 Although a 7-year study of all first-year residents in 1968 suggested that the number of primary care specialists was declining and there was also decreasing popularity of office-based practice as a career, these trends reversed in the 1980s. 13 What is clear in the career development process is that residents' initial career goals do not always materialize as evidenced by a study in which 60% of internal medicine residents who initially considered primary care as their goal changed their decision and chose a subspecialty area instead.14

One of the interesting findings in our survey was that a surprisingly large number of programs (15%) offer no formal, planned counseling in the PL-1 year, but these percentages decrease to 7% and 3%, respectively, in the PL-2 and PL-3 years. Many programs reported 2 or fewer hours of counseling in each year, an inadequate amount of time to assess residents' interests, skills, and values. Although the frequency of meetings with residents does not increase with training, the amount of time spent does, reaching a maximum mean of 5 hours per year. This may be a reasonable amount of time if the resident understands the importance of his or her information gathering in the process.

Respondents were given the opportunity to define and list the process, content, and personnel used in their career counseling programs. Responses suggested that periodic Residency Review Committee-mandated semiannual meetings between residents and program directors occur, with the focus being performance evaluations rather than career counseling.15 Respondents appeared to have difficulty separating out counseling from these evaluations, and time spent in counseling activities actually may have been overestimated. In contrast, those training programs with a more defined curriculum were able to specify how their counseling process works.

An unanticipated finding was the fact that more than one third of the responding programs do not have a formal follow-up process to determine what and how past trainees are doing. Monitoring the long-term outcomes of graduates can be an effective means of posttraining feedback to anticipate the needs of present and future trainees. Former residents can provide RTPDs with their perceptions of the strengths and weaknesses of their training within the context of their careers. These alumni can also be an asset in a practice management curriculum to help prepare residents to enter practice.

Faculty advisors make up the single largest group that provides counseling to residents. Programs reported that the RTPD or chairperson assigns residents to faculty advisors either prior to or after a resident tentatively commits

to a career choice. Since a career decision is made early in one's training, the advisor has to be able to guide the resident in his or her definitive career choice. The survey confirmed that few faculty members are trained in this area and have the necessary expertise to be of maximal assistance in this process.

Respondents considered the knowledge of career options as the No. 1 priority in counseling. The faculty advisor, to fulfill this expectation, has to be aware of an endless number of factors in helping a trainee select a career. For example, knowing the abilities and talents needed in primary care vs academic medicine and how the trainee's attributes "fit" with these requirements is essential information in the counseling process. Is there a typical daily schedule in that area of pediatrics, and if so, what is it like? What are some of the challenges in that area in the next 5 to 10 years, including the projected supply of physicians planning to enter it?

The second highest ranked priority is the counselor's ability to assess the resident's strengths and weakness. None of the respondents stated that their residents perform a self-assessment as an objective means of determining their career paths. This is considered to be the first and probably most important step in the career process.16 Integrating priorities with objective and reliable information obtained from learning preference and personality inventories can be helpful in selecting a career choice. 17-21 Characteristics such as whether the trainee has published research, lived with others, and has other sources of income are additional variables that have been correlated with resident career choice.11 The approach that requires active participation by trainees can help direct them, enlist them as problem-solvers in the process, and provide data on which to base a decision. Once the resident's skills, values, interests, and personality type are established, the counselor and resident may use this information in helping to match the resident with a specific job. Other influencing factors ranked as important by respondents included family, preferred lifestyle, geographic preference, and economics.

The major limitations in counseling as reported by respondents were time and

subjectiveness. If one of the major goals of training programs is to educate adequately residents and provide them with sufficient clinical material to master a given body of knowledge in pediatrics, the next logical progression is to help place them in careers in which they will be productive and happy. With projections of an oversupply of pediatricians in the 1990s and a saturated marketplace in many metropolitan areas, training programs may have to commit even more time to career counseling. Two solutions to the time limitation factor are to encourage the trainee to assume a more active role in the counseling process (eg, completing a selfassessment and analyzing it) and to include more faculty trained in counseling. Both steps would entail an initial investment of time but would improve the process in the long run.

The perceptions of responding programs was that there is a need for improvement in the counseling process. This suggests that programs may be amenable to change and innovation if an effective model can be developed. As a concrete example of change, programs can include in their curricula an office practice rotation that will allow trainees to examine the lifestyle of a practicing pediatrician as a career option. In addition, seminars on what life is like in practice and academia can be beneficial to the trainee. In these sessions, the skills needed to perform effectively in either environment can be demonstrated by role models in the field.

Based on the results of the survey, a number of recommendations are offered to assist training programs in this most important process. These include faculty training, providing options in the curriculum, accessing job market opportunities, and encouraging the Residency Review Committee to examine the career development process in each program to ensure quality and optimal benefit to residents.

Many RTPDs and chairpersons are unable to provide the necessary counseling to residents because of time limitations; hence, the role of faculty advisors. None of the respondents reported having received training in counseling and considered this lack of formal education a barrier. Thus, there is a clear, identified need for faculty development

in the career counseling process. In fact, a model has been established at the undergraduate level; ie, the Glaxo Pathway Evaluation Program (Glaxo Inc, Research Triangle Park, NC). It is based on the vigilant decision-making model reported by Janis and Mann.1 The training occurs in an intensive participatory 21/2-day workshop, and on its completion each participant is qualified to teach these skills to others. Using this or similar methods would ensure greater consistency among faculty and allow the RTPD to delegate more responsibility without concern about compromise in quality.

Many training programs will have to consider curricular changes to provide residents with a wider spectrum of experiences in academic medicine and practice if residents are to make more informed career decisions. This entails extending curricula into the community to allow residents to observe pediatricians "on the job" in a private practice, health maintenance organization, or

other primary care setting.²² In addition, curricula must emphasize the skills needed to succeed in academic life; ie, teaching and research design.²³ A resident unaware of the spectrum of career opportunities cannot make an informed choice in this area. This can lead to unrealistic expectations resulting in burnout and disappointment.

Another problem identified through the survey is the improbable task for any resident counselor to be knowledgeable of the job market within or outside his or her geographic area. A proposed solution would be to develop a central, computerized network to facilitate job placement for residents throughout the country. Counselors and residents would be able to access on-line information on the types, location, and descriptions of practice and academic opportunities available to trainees.

This survey points out that the career counseling process needs to be more formalized and not left up to residents' desires. Whereas one cannot attribute dissatisfaction in a career to inadequate counseling, it seems appropriate for scientists to approach this task using a more valid, theoretical base. The fact is that more objective information can be collected in the career development process of the pediatric resident. Residents must assume the primary responsibility in the decision-making process but faculty need to facilitate this process with more wise counsel and less well-meaning advice.

Finally, although not specifically addressed in this survey, with the increasing number of women entering medicine overall, and more specifically pediatrics, faculty need to be sensitive to the special needs of women.²⁴

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The Howard A. Rusk Institute of Rehabilitation Medicine, New York University Medical Center seeks applicants for the position of pediatric physiatrist. Applicant should be board-certified/-eligible in PM & R, and preferably board-certified/-eligible in pediatrics. Activities include supervision of inpatients in a 35-bed pediatric unit, acute care hospital consultations, supervision of outpatients in subspecialty clinics, resident teaching, and research. Competitive salary/fringe benefits. Send curriculum vitae and three letters of reference to:

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EAST TENNESSEE — BC/BE pediatrician to join three-person group in Morristown. Surrounded by TVA lakes; within fifty miles of Knoxville, Gatlinburg, Great Smoky Mountains. Contact: David V. Willbanks, MD, 403 McFarland, Morristown, TN 37814. (615) 581-3904.

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NEONATOLOGIST needed for Level II university-affiliated intensive care nursery in Philadelphia, Pennsylvania. Responsibilities include resident teaching, clinical duties and clinical research. Appointment to university faculty. Salary commensurate with experience. Contact: Mark Bateman, Executive Vice-President, Episcopal Hospital, Front Street and Lehigh Avenue, Philadelphia, PA 19125. (215) 427-7163.

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LOYOLA UNIVERSITY of Chicago/Neonatology -We are once again expanding our university affiliated neonatology program beginning in 1990. Three positions are available for neonatologists who are interested in the following combined role: attending neonatologist in the university's Level III regional center and in a Level II community pro-gram. You will spend approximately four months in the Level II program and eight months at the university where teaching, clinical research, and attending responsibilities would be carried out. You would join a current staff of sixteen neonatologists. Board certification in neonatology is required except for recent graduates. Please send your curriculum vitae and two letters of recommendation to: Craig L. Anderson, MD, Director, Section of Neonatology, Room 5811, Building 107, Loyola University Medicine Center, 2160 South First Avenue, Maywood, IL 60153. Loyola University of Chicago is an equal opportunity educator and employer. Qualified persons are not subject to discrimination on the basis of a handicap.

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The University of South Dakota School of Medicine currently has openings for the following BE/BC pediatric subspecialties:

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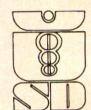
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Special Features

Radiological Case of the Month

T. David Marsh, MD; Laura Farach, MD (Contributors);
Beverly P. Wood, MD (Section Editor)

Accepted for publication May 26, 1989. Contributed from the Department of Pediatrics, Division of Neonatology, Richland Memorial Hospital, Columbia, SC.

Reprint requests to the Department of Radiology, Childrens Hospital of Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90027 (Dr Wood).

A 28-week-gestation black male infant with a birth weight of 1270 g was delivered by cesarean section. After feedings were initiated, the baby developed intermittent feeding intolerance with nonbilious emesis and large gastric aspirates. Plain roentgenograms of the abdomen were normal (Fig 1). The patient was placed on continuous oral gastric feeding and improved slowly. Because of recurring

feeding intolerance and bradycardia, a barium esophagogram was obtained. This study documented an episode of gastroesophageal reflux. The feeding intolerance continued despite treatment of gastroesophageal reflux with bethanechol and aluminum hydroxide (Maalox).

An upper gastrointestinal series was repeated and a view of the stomach and duodenum is shown (Fig 2).



Figure 1.



Figure 2.

Denouement and Discussion

Obstructing Annular Pancreas

Fig 1.—Normal roentgenogram of the ab-

Fig 2.—Upper gastrointestinal series showing rounded obstruction in the second portion of the duodenum (arrow).

Annular pancreas, an uncommon anomaly, is a ring of pancreatic tissue surrounding the second part of the duodenum. Males are affected more frequently than females,1 and the abnormality has been reported in siblings. Annular pancreas has been found in association with pancreatitis, hyperinsulinism, Down syndrome, and congenital heart disease.2 The clinical presentation is varied because of varying amounts of constriction of the duodenum. In some cases, obstruction is complete, and is associated with stenosis or atresia of the duodenum in 40% of the cases. These infants have the typical signs and symptoms of upper gastrointestinal obstruction with bilious or nonbilious vomiting, depending on the position of the ampulla of Vater. Gastric distention and a classic "double bubble" of gas on the roentgenogram of the abdomen are seen. The diagnosis is made by upper gastrointestinal series and has also been made on prenatal ultrasound examination. Differentiation from isolated duodenal atresia is made at surgery.

Feeding intolerance in the premature infant is common and is often attributed to decreased gastrointestinal motility or gastroesophageal reflux.³ A possible clue to an anatomical cause of obstruction is persistent gastric dilatation, noted in a retrospective review of five cases of pyloric stenosis. The differential diagnosis of intestinal obstruction in the newborn includes meconium ileus, intestinal atresias,

midgut volvulus, abdominal masses, Hirschsprung disease, meconium plug syndrome, functional intestinal obstruction, and perinatal appendicitis with perforation.⁴

It is important to consider causes other than gastroesophageal reflux in the differential diagnosis of nonbilious emesis in the neonate.

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Picture of the Month

Susan Buttross, MD, Twila W. Massingale, PhD (Contributors); Murray Feingold, MD (Section Editor)



Figure 1.



Figure 2.



Figure 3.





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Clinic, University of Mississippi Medical Center,
Jackson, Miss.

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Denouement and Discussion

Trisomy 8/Mosaic Syndrome

Fig 1.-Long, narrow trunk, narrow pelvis, and joint contractures.

Fig 2.—Prominent forehead, broad nasal bridge, prominent nares, apparent ocular hypertelorism, and thick lips with everted lower lip.

Fig 3. - Cup-shaped ears with thickened superior helices.

Fig 4. — Deep plantar furrows and camptodactyly of the toes.

Facial features of trisomy 8/mosaic syndrome consist of a prominent fore-head, elongated face, broad nasal bridge, deep-set eyes, abnormally shaped ears with a large auricle and prominent anthelix, thick everted lips, high-arched palate, and micrognathia. The neck may be short, and the trunk is usually long and narrow. Various skeletal malformations are present, including kyphoscoliosis, supernumerary vertebrae and/or ribs, and an abnormally shaped chest. Hand ab-

normalities consist of brachydactyly, clinodactyly, and camptodactyly. Contractures and the absence of patellae have also been reported. Deep palmar and plantar skin furrows are present during infancy. Cryptorchidism and testicular hypoplasia also occur. Varying degrees of mental retardation are present.

Trisomy 8 (no mosaicism) is usually incompatible with life. The cause of the nondisjunction that results in an extra No. 8 chromosome is not known.

As the patient becomes older the number of trisomy 8 cells may decrease, resulting in more cells with a normal number of chromosomes.

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The Editors welcome contributions to Picture of the Month and Radiological Case of the Month. Those who wish to contribute should send their manuscripts to Dr Feingold (Picture of the Month), National Birth Defects Center, Franciscan Children's Hospital, 30 Warren St, Brighton, MA 02135, or Dr Wood (Radiological Case of the Month), Department of Radiology, Childrens Hospital of Los Angeles, 4650 Sunset Blvd, Los Angeles, CA 90027. Articles and photographs accepted for publication will bear the contributor's name. There is no charge for reproduction and printing of color illustrations.



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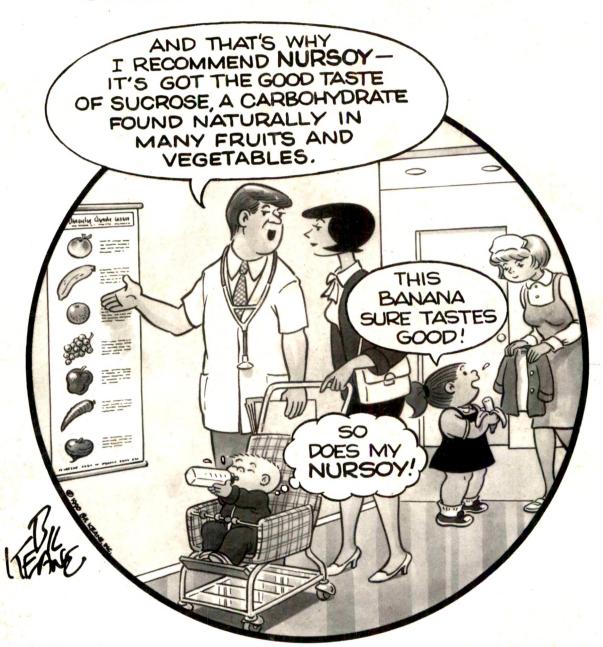
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